I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the U.S. Postal Service on the date shown below with sufficient postage as Express Mail No.: EF077312000US, in an envelope addressed to: Mail Stop Hatch-Waxman PTE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Dated: Aug. 17, 2017 Signature: Lorna L. Tanner (Lorna L. Tanner)

Docket No.: 37JE-192137-US3
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No.: 6,835,739

Issued: December 28, 2004

Confirmation No.: 8779

Inventors: Bing-Yan Zhu, Penglie Zhang, Lingyan Wang, Wenrong Huang, Erick A. Goldman, Wenhao Li, Jingmei Zuckett, Yonghong Song, and Robert M. Scarborough

Assignee: Millennium Pharmaceuticals, Inc.

For: BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Applicant, Millennium Pharmaceuticals, Inc. ("Millennium"), hereby submits this application for extension of the term of U.S. Patent No. 6,835,739 under 35 U.S.C. § 156 by providing the following information in accordance with the requirements specified in 37 C.F.R. § 1.740.

Applicant represents that it is the assignee of the entire interest in and to United States Patent No. 6,835,739, granted to Bing-Yan Zhu, Penglie Zhang, Lingyan Wang, Wenrong Huang, Erick A. Goldman, Wenhao Li, Jingmei Zuckett, Yonghong Song, and Robert M. Scarborough by virtue of an assignment of such patent to Cor Therapeutics, Inc., recorded December 19, 2012, at Reel 029502, Frame 0737, and merger of Cor Therapeutics, Inc., into Millennium Pharmaceuticals, Inc., recorded December 19, 2012, at Reel 029504, Frame 0084.

Portola Pharmaceuticals, Inc. ("Portola"), the licensee of U.S. Patent 6,835,739, was the Marketing Applicant for BEVYXXA®. A letter dated August 16, 2017, from Portola to Millennium specifically authorizes Millennium to rely on Portola's activities in conjunction with this Application. A copy of this letter is attached herewith as Exhibit A.

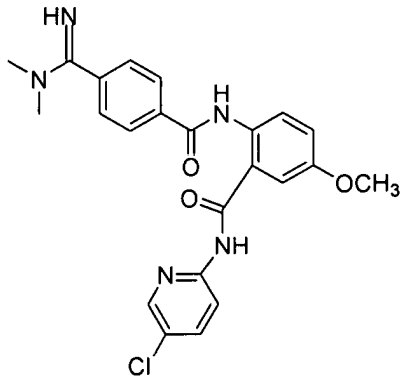
I. A complete identification of the approved product as by appropriate chemical and generical name, physical structure or characteristics (1.740(a)(1))

The United States Food and Drug Administration has approved the New Drug Application ("NDA") 208383 for BEVYXXA® (betrixaban). A copy of the approved labeling is attached herewith as Exhibit B.

The active ingredient of BEVYXXA® is betrixaban. Betrixaban is contained in the drug product as a maleate salt ("betrixaban maleate").

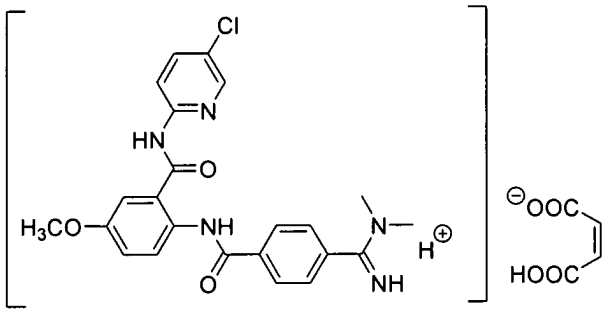
The IUPAC (International Union of Pure and Applied Chemistry) chemical name for betrixaban is *N*-(5-chloropyridin-2-yl)-2-([4-(*N*,*N*-dimethylcarbamimidoyl)benzoyl]amino)-5-methoxybenzamide. Another way to express the chemical name of betrixaban is [2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide, which was used in U.S. Patent No. 6,835,739.

Betrixaban has the following structure:



The molecular formula of betrixaban is $C_{23}H_{22}ClN_5O_3$, and the molecular weight is 451.91 g/mol.

The structure of the maleate salt of betrixaban is shown below:



The molecular formula of the maleate salt is $C_{27}H_{26}ClN_5O_7$, which corresponds to a molecular weight of 567.98 g/mol.

Each capsule of BEVYXXA® contains 40 mg or 80 mg of betrixaban maleate.

II. A complete identification of the Federal Statute including the applicable provision of law under which the regulatory review occurred (1.740(a)(2))

The approved product, BEVYXXA®, was subject to regulatory review under Section 505 of the Federal Food, Drug, and & Cosmetic Act (21 U.S.C. § 355)("FFDCA"). Section 505(b) of the FFDCA, 21 U.S.C. § 355(b), authorizes the filing of an NDA for a "new drug." FDA subsequently approved BEVYXXA® NDA 208383 under the authority granted the agency in Section 505(c) of the FFDCA, 21 U.S.C. § 355(c).

III. An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred (1.740(a)(3))

The FDA approved NDA 208383 for BEVYXXA® for commercial marketing and use under Section 505(b) of the Federal Food, Drug, and & Cosmetic Act (21 U.S.C. § 355) on June 23, 2017. A copy of the letter from the FDA approving marketing of BEVYXXA® is attached as Exhibit C.

IV. In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved (1.740(a)(4))

Betrixaban, the sole active ingredient of BEVYXXA®, has not been previously approved for commercial marketing or use under the Federal Food, Drug, and & Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

V. A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted (1.740(a)(5))

This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the permitted sixty-day time period pursuant to 37 C.F.R. § 1.720(f). The last date this application may be submitted is August 21, 2017.

VI. A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration (1.740(a)(6))

The complete identification of the patent for which extension of term is being sought is as follows:

U.S. Patent No.	6,835,739 ("the '739 Patent")
Inventors	Bing-Yan Zhu, Penglie Zhang, Lingyan Wang, Wenrong Huang, Erick A. Goldman, Wenhao Li, Jingmei Zuckett, Yonghong Song, Robert M. Scarborough
Assignee	Millennium Pharmaceuticals, Inc.
For	Benzamides and related inhibitors of factor Xa
Issued	December 28, 2004
Date of Original Expiration	September 15, 2020

VII. A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings (1.740(a)(7))

A copy of U.S. Patent 6,835,739 is attached as Exhibit D. The patent includes 11 claims and no drawings.

VIII. A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent (1.740(a)(8))

A copy of the U.S. Patent & Trademark Office Maintenance Fee Bibliographic Data is attached as Exhibit E. As shown in this Exhibit, the maintenance fees for U.S. Patent 6,835,739 have been paid, and no maintenance fees are currently due.

A terminal disclaimer was filed on May 27, 2004, in U.S. Patent 6,835,739 disclaiming the terminal part of the statutory term of any patent which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. § 154 and §173 of U.S. Patent 6,376,515. A copy of the disclaimer is attached as Exhibit F.

A copy of the Certificate of Corrections which issued with respect to U.S. Patent 6,835,739 is attached as Exhibit G.

No reexamination certificates have been issued with respect to U.S. Patent 6,835,739.

IX. A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on:

(i) The approved product, if the listed claims include any claim to the approved product;

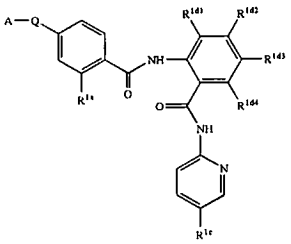
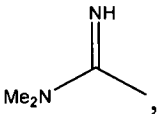
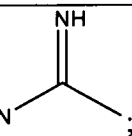
(ii) The method of using the approved product, if the listed claims include any claim to the method of using the approved product; and

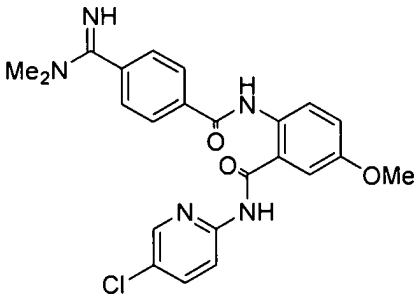
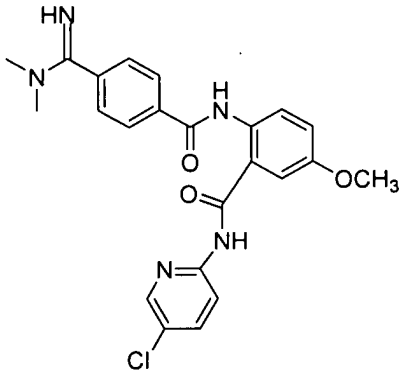
(iii) The method of manufacturing the approved product, if the listed claims include any claim to the method of manufacturing the approved product

(1.740(a)(9))

U.S. Patent 6,835,739 claims the approved product. The '739 Patent includes 11 claims, of which claims 1, 2, and 11 claim betrixaban or a pharmaceutical composition comprising betrixaban.

A claim chart that lists each applicable claim of the '739 Patent and demonstrates the manner in which each claim reads on the approved product is provided below.

Claims of '739 Patent	**Demonstration of the manner in which the claim reads on the approved product or method of using the approved product**
1. A compound having the formula:  wherein: A-Q is a member selected from the group  consisting of: . . . . , ... R^{1a} is a member selected from the group of H, F, Cl and Br; R^{1e} is a member selected from the group consisting of —H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; R^{1d1}, R^{1d2} and R^{1d4} are each H; R^{1d3} is selected from the group consisting of: H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2NMe$, —NHCOMe, —CF_3, —OH, —OCH_3, ... and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.	 When A-Q is ; R^{1a} is H; R^{1e} is —Cl; R^{1d1}, R^{1d2} and R^{1d4} are each H; R^{1d3} is —OCH_3; and the compound is a pharmaceutically acceptable salt; the compound recited in claim 1 is betrixaban. Accordingly, claim 1 reads on the approved product.

Claims of '739 Patent	**Demonstration of the manner in which the claim reads on the approved product or method of using the approved product**
2. A compound of claim 1 structure selected from the group consisting of:  . . . . , ...	Betrixaban has the structure:  Accordingly, claim 2 reads on the approved product.
11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.	Betrixaban (recited in claim 1) is administered as a pharmaceutical composition. Accordingly, claim 11 reads on a pharmaceutical composition comprising the approved product.

X. A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product:

(A) The effective date of the investigational new drug (IND) application and the IND number;

(B) The date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number; and

(C) The date on which the NDA was approved or the Product License issued

(1.740(a)(10))

Pursuant to 35 U.S.C. § 156(g), Applicant provides the following relevant dates and information to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period:

Portola submitted an Investigational New Drug Application (IND), IND 072,679, to the FDA on October 10, 2005, which was received at the FDA on October 12, 2005. The effective date of the IND 072,679 was November 30, 2005, pursuant to 21 C.F.R. § 312.40(b)(2).

Portola's new drug application (NDA) for BEVYXXA® was initially submitted on October 24, 2016, and was approved on June 23, 2017 (NDA 208383).

XI. A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities (1.740(a)(11))

Attached as Exhibit H is a "Summary of Significant Events During Regulatory Review Period." This Exhibit provides a description of the significant activities undertaken by Portola during the applicable regulatory review period with respect to BEVYXXA® and the significant dates applicable to such activities. Applicant (or Portola) reserves the right to supplement the activity described in Exhibit H if further clarification is needed.

XII. A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined (1.740(a)(12))

U.S. Patent 6,835,739 is eligible for a patent term extension under 35 U.S.C. § 156 because:

- one or more claims of the '739 Patent claim the approved product, BEVYXXA®;
- the '739 Patent has not expired;
- the term of the '739 Patent has not been previously extended under 35 U.S.C. § 156;
- the patent term extension application is submitted by the owner of record of the patent, Millennium Pharmaceuticals, Inc.;
- the approved product, BEVYXXA®, has been subject to a regulatory review prior to its commercial marketing or use;
- the approved product, BEVYXXA®, received permission for commercial marketing or use on June 23, 2017, and the application has been submitted within 60 days from the date;
- the permission for the commercial marketing or use of the approved product, BEVYXXA®, after the regulatory review period is the first permitted commercial marketing or use under the provisions under which the regulatory review period occurred; and
- no other patent term has been extended for the same regulatory review period for the approved product, BEVYXXA®.

The length of extension claimed is 5 years and is calculated as follows:

The original expiration date of the patent from which the patent term extension will run is September 15, 2020.

The regulatory review period was calculated as the sum of paragraphs 1 and 2 below:

1. the number of days from the effective date of the IND (November 30, 2005) to the filing of the NDA (October 24, 2016), which is a total of 3982 days; and

2. the number of days from the filing of the NDA (October 24, 2016), to the date of the approval of the NDA (June 23, 2017), which is a total of 243 days.

The regulatory review period is 4225 days.

The term that the patent is extended is generally determined under 37 C.F.R. § 1.775(d) by subtracting from the number of days determined to be the regulatory review period, the following:

a. the number of days in the regulatory review period which were on or before the date on which the patent issued, which is 0 days (corresponding to effective IND date of November 30, 2005 to the issue date of December 28, 2004 for the '739 Patent);

b. the number of days in the regulatory review period in which it is determined that the applicant did not act with due diligence, which is 0 days; and

c. one half of the number of days determined in paragraph 1 above less the number of days between paragraph 1 and the issue date of December 28, 2004 for the '739 Patent and less the number of days in which it is determined that the applicant did not act with due diligence, which is a total of 1991 days.

The calculation under 37 C.F.R. § 1.775(d)(1) is as follows:

4225 days – 0 days – 0 days – 1991 days = 2234 days

When 2234 days are added to the original expiration date of the '739 Patent, the resulting date of expiration would be October 28, 2026.

However, the date to which the patent may be extended cannot exceed the earlier of 14 years from the date of the NDA approval or, since the '739 Patent issued after September 24, 1984, five years from the original expiration date of the patent:

14 years from NDA Approval Date of June 23, 2017: June 23, 2031

5 years from Original Expiration Date: September 15, 2025

Therefore, the maximum extension available is 5 years, and the '739 patent should expire on September 15, 2025.

XIII. A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought (1.740(a)(13))

Applicant hereby acknowledges its duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

XIV. The prescribed fee for receiving and acting upon the application for extension (1.740(a)(14))

The payment of the fee prescribed in 37 C.F.R. § 1.20(j) for a patent term extension application under 35 U.S.C. § 156 accompanies this application. Please deduct any additional required fees from, or credit any overpayment, to deposit account No. 50-6219.

XV. The name, address, and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed (1.740(a)(15))

Please direct all correspondence and inquiries to the following:

Lorna L. Tanner
SHEPPARD MULLIN RICHTER & HAMPTON LLP
379 Lytton Avenue
Palo Alto, CA 94301
Tel.: (650) 815-2600
Fax: (650) 815-2601
Email: svipdocketing@sheppardmullin.com

XVI. Certification under 37 C.F.R. §§1.740(b)

The original and two duplicate copies of the application, totaling three copies, are being submitted. It is hereby certified that the copies are identical to the original.

In view of the foregoing, Applicant requests that the Director grant an extension of 5 years to the term of U.S. Patent No. 6,835,739.

Dated: Aug. 17, 2017

Respectfully submitted,

By Lorna L Tanner

Lorna L. Tanner
Registration No.: 50,782
SHEPPARD MULLIN RICHTER & HAMPTON LLP
379 Lytton Avenue
Palo Alto, California 94301
(650) 815-2600
Attorney For Applicant

Exhibit A

PORTOLA PHARMACEUTICALS
info@portola.com | T: 650.246.7000 | 270 East Grand Avenue
www.portola.com | F: 650.246.7376 | South San Francisco, CA 94080

Innovative Science. Patient Focused.

August 16, 2017

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RE: Letter Authorizing Reliance on Activities of the Marketing Applicant
U.S. Patent No. 6,835,739
Issued: December 28, 2004
Assignee: Millennium Pharmaceuticals, Inc.

Dear Commissioner:

Portola Pharmaceuticals, Inc. (the Marketing Applicant before the Food and Drug Administration for the approved drug product, BEVYXXA® (IND 072,679; NDA 208383)) hereby specifically authorizes Millennium Pharmaceuticals, Inc., the assignee of U.S. Patent No. 6,835,739, to rely upon the activities of Portola Pharmaceuticals, Inc. before the Food and Drug Administration in conjunction with Millennium Pharmaceuticals, Inc.'s application for patent term extension. This letter is provided pursuant to M.P.E.P. §2752.

Sincerely,

John T. Curnutte, M.D., Ph.D.
Executive Vice President, Research and Development

cc: Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge MA 02139

Exhibit B

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BEVYXXA safely and effectively. See full prescribing information for BEVYXXA.

BEVYXXA ™ (betrixaban) capsules, for oral use
Initial U.S. Approval: 2017

WARNING: SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (5.2)

INDICATIONS AND USAGE

BEVYXXA is a factor Xa (FXa) inhibitor indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. (1)

Limitations of Use:
Safety and efficacy of BEVYXXA have not been established in patients with prosthetic heart valves because this population has not been studied. (1)

DOSAGE AND ADMINISTRATION

The recommended dose of BEVYXXA is an initial single dose of 160 mg, followed by 80 mg once daily, taken at the same time each day with food. The recommended duration of treatment is 35 to 42 days. (2.1)

- Reduce dose for patients with severe renal impairment. (2.2)
- Reduce dose for patients on P-glycoprotein (P-gp) inhibitors. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 40 mg and 80 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding. (4)
- Severe hypersensitivity reaction to betrixaban BEVYXXA. (4)

WARNINGS AND PRECAUTIONS

- Risk of Bleeding: Can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.1)
- Severe Renal Impairment: Increased risk of bleeding events; reduce BEVYXXA dose (2.2, 5.3)
- Concomitant P-gp Inhibitors: Increased risk of bleeding events; reduce BEVYXXA dose (2.3, 5.4)

ADVERSE REACTIONS

Most common adverse reaction (incidence >5%) is bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Portola Pharmaceuticals at 1-855-767-7167 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- P-gp inhibitors increase the blood levels of betrixaban. Reduce BEVYXXA dose. (7.1)
- Anticoagulants: Avoid concomitant use. (7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if potential benefit outweighs the potential risk to the mother or fetus (8.1)
- Renal Impairment: Reduce dose. (8.6)
- Hepatic impairment: Avoid use (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2017

FULL PRESCRIBING INFORMATION: CONTENTS *

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

BEVYXXA is indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE *[see Clinical Studies (14)]*.

Limitations of Use:

The safety and effectiveness of BEVYXXA have not been established in patients with prosthetic heart valves because this population has not been studied.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of BEVYXXA is an initial single dose of 160 mg, followed by 80 mg once daily. Daily oral doses should be given at the same time of day with food.

The recommended duration of treatment is 35 to 42 days.

2.2 Severe Renal Impairment

For patients with severe renal impairment (CrCl $\geq$ 15 to $<$ 30 mL/min computed by Cockcroft-Gault using actual body weight) the recommended dose of BEVYXXA is an initial single dose of 80 mg followed by 40 mg once daily *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6), Clinical Pharmacology (12.3]*. The recommended duration of treatment is 35 to 42 days.

2.3 Use with P-gp Inhibitors

For patients receiving or starting concomitant P-gp inhibitors the recommended dose of BEVYXXA is an initial single dose of 80 mg followed by 40 mg once daily *[see Warnings and Precautions (5.4), Drug Interactions (7.1), Clinical Pharmacology (12.3)]*. The recommended duration of treatment is 35 to 42 days.

2.4 Missed Dose

If a dose of BEVYXXA is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. The BEVYXXA dose should not be doubled to make up for a missed dose.

3 DOSAGE FORMS AND STRENGTHS

40 mg and 80 mg capsules

- 80 mg, size 2 hard gelatin capsules are light grey with 80 printed in black, and have a blue cap with PTLA printed in white.
- 40 mg, size 4 hard gelatin capsules are light grey with 40 printed in black, and have a light blue cap with PTLA printed in white.

4 CONTRAINDICATIONS

BEVYXXA is contraindicated in patients with:

- Active pathological bleeding *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*
- Severe hypersensitivity reaction to betrixaban *[see Adverse Reactions (6.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding

BEVYXXA increases the risk of bleeding and can cause serious and potentially fatal bleeding. Promptly evaluate any signs or symptoms of blood loss *[see Adverse Reactions (6.1)]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.2)]*.

Advise patients of signs and symptoms of blood loss and to report them immediately and seek emergency care. Promptly evaluate any signs or symptoms of blood loss and consider the need for blood replacement. Discontinue BEVYXXA in patients with active pathological bleeding.

There is no established way to reverse the anticoagulant effect of BEVYXXA, which can be expected to persist for at least 72 hours after the last dose. It is unknown whether hemodialysis removes BEVYXXA. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of BEVYXXA.

5.2 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

Do not remove an epidural catheter earlier than 72 hours after the last administration of BEVYXXA. Do not administer the next BEVYXXA dose earlier than 5 hours after the removal of the catheter. If traumatic puncture occurs, delay the administration of BEVYXXA for 72 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention, consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

5.3 Use in Patients with Severe Renal Impairment

Patients with severe renal impairment (CrCl $\geq$ 15 to < 30 mL/min computed by Cockcroft-Gault using actual body weight) taking BEVYXXA may have an increased risk of bleeding events. Reduce dose of BEVYXXA, monitor patients closely, and promptly evaluate any signs or symptoms of blood loss in these patients *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6.1), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

5.4 Use in Patients on Concomitant P-gp Inhibitors

Patients on concomitant P-gp inhibitors with BEVYXXA may have an increased risk of bleeding. Reduce dose of BEVYXXA in patients receiving or starting P-gp inhibitors. Monitor patients closely and promptly evaluate any signs or symptoms of blood loss in these patients *[see Dosage and Administration (2.3), Warnings and Precautions (5.1), Adverse Reactions (6.1), Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Avoid use of BEVYXXA in patients with severe renal impairment receiving concomitant P-gp inhibitors *[see Warnings and Precautions (5.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Risk of Bleeding *[see Warnings and Precautions (5.1, 5.3, 5.4)]*.
- Spinal/Epidural Anesthesia or Puncture *[see Boxed Warning and Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of BEVYXXA was evaluated in the Acute Medically Ill Prevention with Extended Duration Betrixaban (APEX) Study *[see Clinical Studies (14)]*, including 3,716 patients treated with BEVYXXA for a median of 36 days compared to 3,716 patients treated with enoxaparin for a median of 9 days. Patients in both treatment groups were followed for safety, including bleeding events, for up to 77 days.

Patients randomized to the BEVYXXA arm received BEVYXXA 160 mg orally on Day 1, then 80 mg once daily for 35 to 42 days AND enoxaparin subcutaneous *placebo* once daily for 6 to 14 days. Patients randomized to the enoxaparin arm received enoxaparin 40 mg subcutaneously once daily for 6 to 14 days AND BEVYXXA *placebo* orally once daily for 35 to 42 days.

Patients with severe renal impairment (creatinine clearance $\geq$ 15 and < 30 mL/min) received reduced doses of study medications (BEVYXXA 80 mg loading dose, then 40 mg once daily or enoxaparin 20 mg once daily) along with corresponding placebo.

Patients taking a concomitant P-gp inhibitor received BEVYXXA 80 mg loading dose, then 40 mg once daily or enoxaparin 40 mg subcutaneously once daily for 6 to 14 days along with corresponding placebo.

Hemorrhage

The most common adverse reactions with BEVYXXA were related to bleeding (> 5%) with major bleeding occurring in less than 1% of patients (see Table 1).

Overall, 54% of patients receiving BEVYXXA experienced at least one adverse reaction vs. 52% with enoxaparin. The frequency of patients reporting serious adverse reactions was similar between BEVYXXA (18%) and enoxaparin (17%). In the APEX trial, the most frequent reason for treatment discontinuation was bleeding, with an incidence rate of 2.4% for BEVYXXA vs. 1.2% for enoxaparin.

The primary and secondary safety outcomes in APEX were bleeding-related events.

A summary of major and clinically relevant non-major (CRNM) bleeding events in the overall safety population is shown in Table 1. Most CRNM events (86%) were mild to moderate in severity, and the majority (62%) did not require medical intervention.

The incidence of fatal bleeding was the same in the BEVYXXA and enoxaparin treatment groups (1 in each group).

Table 1: Bleeding Events in APEX through 7 days after Discontinuation of All Study Drugs (Safety Population)

Parameter	BEVYXXA (N=3,716)	Enoxaparin (N=3,716)	BEVYXXA vs. Enoxaparin RR (95% CI)
Major Bleeding [a]	25 (0.67)	21 (0.57)	1.19 (0.67, 2.12) p = 0.554
Gastrointestinal (GI)	19 (0.51)	9 (0.24)	
Intracranial Hemorrhage	2 (0.05)	7 (0.19)	
Intraocular	0 (0)	1 (0.03)	
Fatal Bleeding	1 (0.03)	1 (0.03)	
Clinically Relevant Non-Major Bleeding [b]	91 (2.45)	38 (1.02)	2.39 (1.64, 3.49) p < 0.001

[a] Major bleeding event was defined as clinically overt bleeding that met one of the following criteria: a reduction in hemoglobin of a least 2 g/dL within 48 hours of an overt bleeding event; a transfusion of at least two units of whole blood or packed red blood cells; a critical area; e.g., intraocular, intracranial, intraspinal, intramuscular with compartment syndrome, retroperitoneal, intra-articular, pericardial, or a fatal outcome. Retinal hemorrhages secondary to diabetic retinopathy or conjunctival bleeds did not qualify as a major bleeds.

[b] CRNM bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary/permanent) cessation of the study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.

A summary of major and CRNM bleeding events by dose is shown in Table 2 and Table 3.

Table 2: Summary of Adjudicated Major, CRNM, Major or CRNM Bleeding Events through 7 Days after Discontinuation for Patients Receiving 80 mg

Parameter	BEVYXXA 80 mg (N=2,986) n (%)	Enoxaparin 40 mg (N=2,991) n (%)
Major	15 (0.50)	16 (0.53)
RR (95% CI)	0.94 (0.47, 1.90)	
Clinically Relevant Non-Major (CRNM)	66 (2.21)	33 (1.10)
RR (95% CI)	2.00 (1.32, 3.03)	
Major or CRNM	81 (2.71)	49 (1.64)
RR (95% CI)	1.66 (1.17, 2.35)	

Table 3: Summary of Adjudicated Major, CRNM, Major or CRNM Bleeding Events through 7 Days after Discontinuation for Patients Receiving 40 mg

	Severe Renal Impairment		Concomitant use of P-gp Inhibitor	
Parameter	**BEVYXXA 40 mg (N=150) n (%)**	**Enoxaparin 20 mg (N=125) n (%)**	**BEVYXXA 40 mg (N=542) n (%)**	**Enoxaparin 40 mg (N=527) n (%)**
Major	3 (2.00)	1 (0.80)	6 (1.11)	4 (0.76)
RR (95% CI)	2.5 (0.26, 23.74)		1.46 (0.41, 5.14)	
Clinically Relevant Non-Major (CRNM)	6 (4.00)	2 (1.60)	20 (3.69)	3 (0.57)
RR (95% CI)	2.5 (0.51, 12.17)		6.5 (1.94, 21.68)	
Major or CRNM	9 (6.00)	3 (2.40)	26 (4.80)	7 (1.33)
RR (95% CI)	2.5 (0.69, 9.04)		3.6 (1.58, 8.25)	

The most common adverse reactions occurring in ≥ 2% of patients are shown in Table 4.

Table 4: Adverse Reactions in APEX Occurring in ≥ 2% of Patients

Adverse Reaction	BEVYXXA N=3,716 (n%)	Enoxaparin N=3,716 (n%)
Bleeding-Related (all sources)		
Epistaxis	58 (2)	24 (1)
Hematuria	62 (2)	28 (1)
Non Bleeding Adverse Reaction		
Urinary Tract Infection	123 (3)	87 (2)
Constipation	110 (3)	102 (3)
Hypokalemia	93 (3)	84 (2)
Hypertension	89 (2)	80 (2)
Headache	74 (2)	59 (2)
Nausea	67 (2)	56 (2)
Diarrhea	64 (2)	61 (2)

Other Adverse Reactions

Hypersensitivity reactions: one patient experienced a serious adverse reaction of moderate hypersensitivity

7 DRUG INTERACTIONS

7.1 Inhibitors of P-gp

BEVYXXA is a substrate of P-gp and concomitant use of P-gp inhibitors (e.g., amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin) results in an increased exposure of BEVYXXA *[see Clinical Pharmacology (12.3)]*.

Reduce the dose of BEVYXXA for patients receiving or starting concomitant P-gp inhibitors *[see Dosage and Administration (2.3), Warnings and Precautions (5.4), Clinical Pharmacology (12.3)]*.

7.2 Anticoagulants, Antiplatelets, and Thrombolytics

Co-administration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding. Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with anticoagulants, aspirin, other platelet aggregation inhibitors, and/or NSAIDs *[see Warnings and Precautions (5.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with the use of BEVYXXA in pregnant women, but treatment is likely to increase the risk of hemorrhage during pregnancy and delivery *(see Clinical Considerations)*. Betrixaban was studied in reproductive and developmental toxicology studies in rats and rabbits during the period of organogenesis at exposures up to 44 times the recommended clinical dose of 80 mg daily. Although betrixaban was not associated with adverse developmental fetal outcomes in animals, maternal toxicity (i.e., hemorrhage) was identified in these studies *(see Data)*. BEVYXXA should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

Embryo-fetal development studies were conducted in pregnant rats and rabbits during the period of organogenesis. In rats, no adverse embryofetal or teratogenic effects were seen when betrixaban was administered orally at doses up to 200 mg/kg/day, or 44 times the human dose of 80 mg/day when based on AUC. In rabbits, no adverse embryofetal or teratogenic effects were seen at doses up to 45 mg/kg/day, or 35 times the human exposure at a dose of 80 mg/day when based on AUC. Pregnant rabbits administered the highest dose of 150 mg/kg/day were terminated prematurely due to excessive maternal toxicities. Upon post-mortem examination, early and/or late resorptions and fetal deaths were observed at the 150 mg/kg dose, which may be linked to hemorrhage observed in various organs including the reproductive tract.

In a rat pre-and post-natal developmental study, betrixaban was administered orally during the period of organogenesis and through lactation day 20 at doses up to 200 mg/kg/day. Maternal toxicities (including decreased body weight gain and food consumption and red/brown perivaginal substance) were observed at 200 mg/kg/day, which is approximately 44 times the human exposure when based on AUC. At a maternal dose up to 200 mg/kg/day, betrixaban did not have adverse effects on sexual maturation, reproductive performance, and behavioral development of the F1 generation.

Clinical Considerations

Maternal Adverse Reactions

Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. Consider the risks of bleeding and of stroke in using BEVYXXA in this setting.

8.2 Lactation

Risk Summary

No data are available regarding the presence of betrixaban or its metabolites in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BEVYXXA and any potential adverse effects on the breast-fed child from BEVYXXA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in the APEX clinical study 90% were 65 years and over, while 68.6% were greater than or equal to 75 years. No clinically significant differences in safety or effectiveness were observed between older and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (CrCl $\geq$ 15 to < 30 mL/min computed by Cockcroft-Gault using actual body weight) may have an increased risk of bleeding events. Reduce the BEVYXXA dose for patients with severe renal impairment. Monitor patients closely and promptly evaluate any signs or symptoms of blood loss in these patients *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), Clinical Pharmacology (12.3)]*. No dose adjustment is needed for mild or moderate renal impairment (CrCl > 30 mL/min, computed by Cockcroft-Gault using actual body weight).

8.7 Hepatic Impairment

BEVYXXA has not been evaluated in patients with hepatic impairment, because these patients may have intrinsic coagulation abnormalities. Therefore, the use of BEVYXXA is not recommended in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

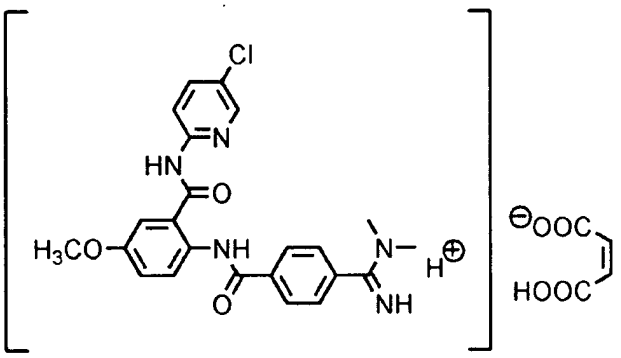
10 OVERDOSAGE

Overdose of BEVYXXA increases the risk of bleeding *[see Warnings and Precautions (5.1)]*.

A specific reversal agent for BEVYXXA is not available. There is no experience with hemodialysis in individuals receiving betrixaban. Protamine sulfate, vitamin K, and tranexamic acid are not expected to reverse the anticoagulant activity of betrixaban.

11 DESCRIPTION

Betrixaban, a factor Xa (FXa) inhibitor, is chemically described as N-(5-chloropyridin-2-yl)-2-[4-(N,N-dimethylcarbamimidoyl)-benzoylamino]-5-methoxybenzamide maleate. Its molecular formula (as maleate salt) is $C_{27}H_{26}ClN_5O_7$, which corresponds to a molecular weight of 567.98. Betrixaban (maleate salt) has the following structural formula:



BEVYXXA capsules are available for oral administration in strengths of 80 mg and 40 mg of betrixaban with the following inactive ingredients: dextrose monohydrate, croscarmellose sodium, magnesium stearate, and a hard gelatin capsule.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Betrixaban is an oral FXa inhibitor that selectively blocks the active site of FXa and does not require a cofactor (such as Anti-thrombin III) for activity. Betrixaban inhibits free FXa and prothrombinase activity. By directly inhibiting FXa, betrixaban decreases thrombin generation (TG). Betrixaban has no direct effect on platelet aggregation.

12.2 Pharmacodynamics

Inhibition of FXa by betrixaban results in an inhibition of thrombin generation at clinically relevant concentrations, and the maximum inhibition of thrombin generation coincides with the time of peak betrixaban concentrations.

Cardiac Electrophysiology

In a study that evaluated the effect of betrixaban on the QT interval, a concentration-dependent increase in the QTc interval was observed. Based on the observed concentration-QTc relationship a mean (upper 95% CI) QTc prolongation of 4 ms (5 ms) is predicted for 80 mg betrixaban and 13 ms (16 ms) for a 4.7-fold increase in exposure *[see Clinical Pharmacology (12.3)]*.

12.3 Pharmacokinetics

Within the anticipated therapeutic dose range a two-fold increase in dose resulted in a three-fold increase in exposure in the single ascending dose study. A two-fold increase in betrixaban exposure was observed after repeat dosing, and the time to steady-state is 6 days (without an initial loading dose).

Absorption

The oral bioavailability of betrixaban for an 80 mg dose is 34%, and peak concentrations occurred within 3 to 4 hours. Betrixaban is also a substrate of P-gp.

Effect of Food

When administered with a low-fat (900 calories, 20% fat) or high-fat (900 calories, 60% fat) meal, C_{max} and AUC were reduced as compared to the fasting state by an average of 70% and 61% for low-fat and 50% and 48% for high-fat, respectively. The effect of food on betrixaban PK could be observed for up to 6 hours after meal intake.

Distribution

The apparent volume of distribution is 32 L/kg. *In vitro* plasma protein binding is 60%.

Elimination

The effective half-life of betrixaban is 19 to 27 hours.

Metabolism

Unchanged betrixaban is the predominant component found in human plasma. Two inactive major metabolites formed by CYP-independent hydrolysis comprise the other components in plasma, accounting for 15 to 18% of the circulating drug-related material. Less than 1% of the minor metabolites could be formed via metabolism by the following CYP enzymes; 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, and 3A4.

Excretion

Following oral administration of radio-labeled betrixaban approximately 85% of the administered compound was recovered in the feces and 11% recovered in the urine. In a study of

intravenous betrixaban a median value of 17.8% of the absorbed dose was observed as unchanged betrixaban in urine.

Specific Populations

Male and Female Patients

No clinically significant changes in betrixaban pharmacokinetics were observed between males and females.

Patients with Renal Impairment

In a dedicated renal impairment study mean AUC_{0-24} on day 8 was increased by 1.89, 2.27 and 2.63-fold in mild ($eGFR_{MDRD} \geq 60$ to < 90 mL/min/1.73 m^2), moderate ($eGFR_{MDRD} \geq 30$ to < 60 mL/min/1.73 m^2) and severe renal ($eGFR_{MDRD} \geq 15$ to < 30 mL/min/1.73 m^2) impaired patients respectively compared to healthy volunteers *[see Use in Specific Populations (8.6)]*.

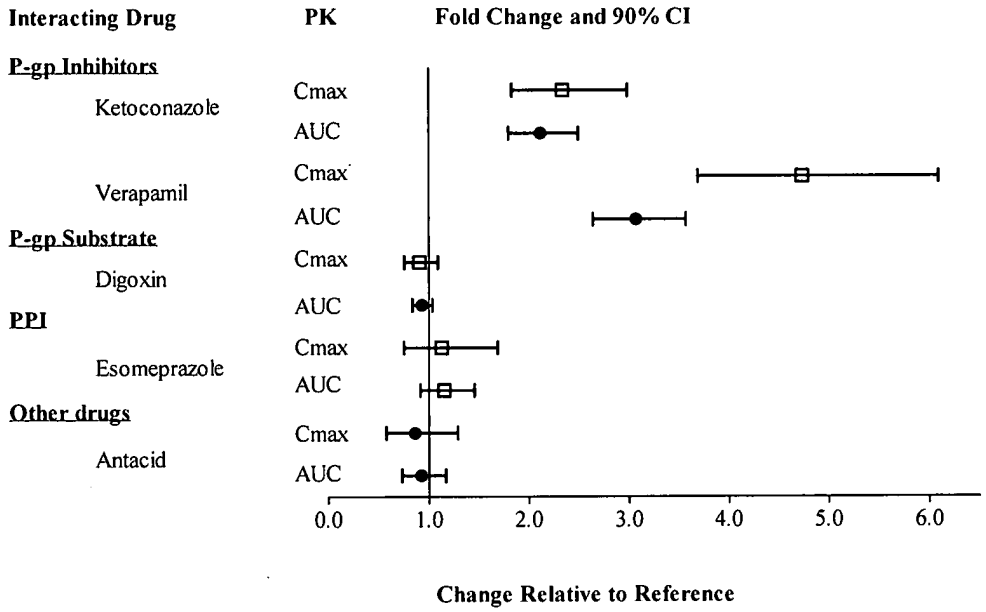
Patients with Hepatic Impairment

Studies with betrixaban in patients with hepatic impairment have not been conducted and the impact of hepatic impairment on the exposure to betrixaban has not been evaluated *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

The effects of coadministered drugs on the pharmacokinetics of betrixaban exposure based on drug interaction studies are summarized in Figure 1.

Figure 1: Effect of Coadministered Drugs on the Pharmacokinetics of Betrixaban



Dedicated Phase 1 studies evaluated the effect of co-administration of other drugs on the PK properties of betrixaban. The reference value in this case is the betrixaban PK parameter (Cmax or AUC) in the absence of the co-administered drug. The only drugs that affected betrixaban concentrations were P-gp inhibitors.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with betrixaban have not been performed.

Betrixaban was not mutagenic in bacteria (Ames-Test) or clastogenic in Chinese hamster ovary cells *in vitro* or in the rat micronucleus test *in vivo*.

In a study to assess fertility and early embryonic development to implantation, oral doses of betrixaban were administered to male and female rats. There was no evidence that betrixaban up to 150 mg/kg/day adversely affected male or female fertility, reproductive performance, or embryo-fetal viability.

14 CLINICAL STUDIES

The clinical evidence for the effectiveness of BEVYXXA is derived from the APEX clinical trial [NCT01583218]. APEX was a randomized, double-blind, multinational study comparing extended duration BEVYXXA (35 to 42 days) to short duration of enoxaparin (6 to 14 days) in

the prevention of venous thromboembolic events (VTE) in an acutely medically ill hospitalized population with risk factors for VTE.

Eligible patients included adults who were at least 40 years of age, hospitalized for an acute medical illness, at risk for VTE due to moderate or severe immobility, and had additional risk factors for VTE (described below). Expected duration of hospitalization was at least 3 days and patients were expected to be moderately or severely immobilized for at least 24 hours. The causes for hospitalization included heart failure, respiratory failure, infectious disease, rheumatic disease, or ischemic stroke. At study initiation eligible patients were required to have one of the following additional risk factors for VTE:

a. $\geq$ 75 years of age,
b. 60 through 74 years of age with D-dimer $\geq$ 2 ULN, or
c. 40 through 59 years of age with D-dimer $\geq$ 2 ULN and a history of either VTE or cancer.

A total of 7,513 patients were randomized 1:1 to:

- BEVYXXA arm (BEVYXXA 160 mg orally on Day 1, then 80 mg once daily for 35 to 42 days AND enoxaparin subcutaneous *placebo* once daily for 6 to 14 days),

  OR

- Enoxaparin arm (enoxaparin 40 mg subcutaneously once daily for 6 to 14 days AND BEVYXXA *placebo* orally once daily for 35 to 42 days).

Patients with severe renal impairment (creatinine clearance $\geq$ 15 and < 30 mL/min) received reduced doses of study medications (BEVYXXA 80 mg loading dose, then 40 mg once daily or enoxaparin 20 mg once daily) along with corresponding placebo.

Patients taking a concomitant P-gp inhibitor received BEVYXXA 80 mg loading dose, then 40 mg once daily or enoxaparin 40 mg subcutaneously once daily for 6 to 14 days along with corresponding placebo.

Baseline characteristics were balanced between the treatment groups. The population was 55% female, 93% White, 2% Black, 0.2% Asian, and 5% others. The most prevalent acute medical illness at hospitalization was acutely decompensated heart failure (45%), followed by acute infection without septic shock (29%), acute respiratory failure (12%), acute ischemic stroke (11%) and acute rheumatic disorders (3%). The mean and median ages were 76.4 and 77 years, respectively, with 68% of patients $\geq$ 75 years of age, 97% were severely immobilized at study entry, and 62% had D-dimer $\geq$ 2 x ULN.

While the APEX Study was ongoing (after 35% enrollment), the study was amended to restrict further enrollment to patients ≥ 75 years of age or with D-dimer values ≥ 2 x ULN. The APEX trial excluded patients whose condition required prolonged anticoagulation (e.g., concurrent VTE, atrial fibrillation, cardiac valve prosthesis), were at increased risk of bleeding, had liver dysfunction, were on dual antiplatelet therapy, or patients who had both severe renal insufficiency (CrCl 15-29 ml/min) and required the concomitant use of a P-gp inhibitor.

The efficacy of BEVYXXA was based upon the composite outcome of the occurrence of any of the following events up to Day 35 visit:

- Asymptomatic proximal Deep Vein Thrombosis (DVT) (detected by ultrasound),
- Symptomatic proximal or distal DVT,
- Non-fatal Pulmonary Embolism (PE), or
- VTE-related death.

Efficacy analyses were performed based on the modified Intent-to-Treat (mITT) population. The mITT population consisted of all patients who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy outcome components. A total of 7,441 patients (N=3,721 for BEVYXXA and N=3,720 for enoxaparin) were included in the mITT population.

The efficacy results for the APEX trial are provided in Table 5 below.

Table 5: Efficacy Outcomes in APEX Trial (mITT Population)

	BEVYXXA N=3,721 n (%) [1]	**Enoxaparin** N=3,720 n (%) [1]	**Relative Risk** (95% CI) [2]
Composite Outcome	165 (4.4)	223 (6.0)	0.75 (0.61, 0.91)
Asymptomatic Event	133 (3.6)	176 (4.7)	
Symptomatic DVT	14 (0.4)	22 (0.6)	
Non-fatal PE	9 (0.2)	18 (0.5)	
VTE-related Death	13 (0.3)	17 (0.5)	
Symptomatic Events [3]	35 (0.9)	54 (1.5)	0.64 (0.42, 0.98)

[1] Percentages and event rates are based on the total number of patients and events included in each treatment group.

[2] Relative Risk (BEVYXXA arm versus enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing strata and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.

[3] Symptomatic events include symptomatic DVT, non-fatal PE or VTE-related death.

For patients with D-dimer ≥ 2 ULN at baseline, the event rate is 5.7% in the BEVYXXA arm vs. 7.2% in the enoxaparin arm (relative risk = 0.79, 95% CI [0.63, 0.98]).

For patients with D-dimer ≥ 2 ULN at baseline or age ≥ 75 years, the event rate is 4.7% in the BEVYXXA arm vs. 6.0% in the enoxaparin arm (relative risk = 0.78, 95% CI [0.64, 0.96]).

Results for the primary efficacy analysis for subjects that were stratified at randomization to the 80 mg BEVYXXA dose group in the mITT population are shown in Table 6 below.

Patients who were randomized to receive 40 mg BEVYXXA (those with severe renal impairment or receiving P-gp inhibitors), had VTE rates similar to the enoxaparin arm (6 to 14 days followed by placebo) shown in Table 7 below.

Table 6: Efficacy Outcomes in APEX Trial (mITT Population) – Patients Stratified to 80 mg BEVYXXA Dose [4]

	BEVYXXA N=2,878 n (%) [1]	**Enoxaparin** N=2,926 n (%) [1]	**Relative Risk** (95% CI) [2]
Composite Outcome	120 (4.2)	180 (6.2)	0.68 (0.55, 0.86)
Asymptomatic Event	100 (3.5)	146 (5.0)	
Symptomatic DVT	11 (0.4)	17 (0.6)	
Non-fatal PE	4 (0.1)	14 (0.5)	
VTE-related Death	8 (0.3)	12 (0.4)	
Symptomatic Events [3]	22 (0.8)	41 (1.4)	0.55 (0.33, 0.92)

[1] Percentages and event rates are based on the total number of patients and events included in each treatment group and stratified to 80 mg dose.

[2] Relative Risk (BEVYXXA arm versus enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing strata and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.

[3] Symptomatic events include symptomatic DVT, non-fatal PE, or VTE-related death.

[4] Analysis excludes patients with severe renal impairment or were receiving P-gp inhibitors.

Table 7: Efficacy Outcomes in APEX Trial (mITT Population) – Patients Stratified to 40 mg BEVYXXA Dose

	Severe Renal Impairment			Concomitant use of P-gp Inhibitor		
	BEVYXXA N=174 n (%) [1]	**Enoxaparin** N=149 n (%) [1]	**Relative Risk** (95% CI)	**BEVYXXA** N=669 n (%) [1]	**Enoxaparin** N=645 n (%) [1]	**Relative Risk** (95% CI)[2]
Composite Outcome	12 (6.9)	10 (6.7)	1.0 (0.45, 2.23)	33 (4.9)	33 (5.1)	1.0 (0.63, 1.60)
Asymptomatic Event	9 (5.2)	7 (4.7)		24 (3.6)	23 (3.6)	
Symptomatic DVT	0	1 (0.7)		3 (0.4)	4 (0.6)	
Non-fatal PE	2 (1.1)	2 (1.3)		3 (0.4)	2 (0.3)	
VTE-related Death	2 (1.1)	0		3 (0.4)	5 (0.8)	
Symptomatic Events [3]	4 (2.3)	3 (2.0)		9 (1.3)	10 (1.6)	

[1] Percentages and event rates are based on the total number of patients and events included in each treatment group by dosing criteria.

[2] Relative Risk (BEVYXXA arm versus enoxaparin arm) is based on the Mantel-Haenszel test stratified by the dosing strata and D-dimer status from the local laboratory. The analyses are not adjusted for multiplicity.

[3] Symptomatic events include symptomatic DVT, non-fatal PE, or VTE-related death.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

BEVYXXA (betrixaban) capsules are available as listed below.

The 40 mg size 4 capsules are light grey with 40 printed in black, and have a light blue cap with PTLA printed in white.

- Bottles of 100 (NDC 69853-0202-1)

The 80 mg size 2 capsules are light grey with 80 printed in black, and have a blue cap with PTLA printed in white.

- Bottles of 100 (NDC 69853-0201-1)

Storage and Handling

Store at room temperature; 20°C to 25°C (68°F to 77°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Risk of Bleeding

Advise patients that it might take longer than usual for bleeding to stop, and that they may bruise or bleed more easily when treated with BEVYXXA. Instruct patients to report any unusual bleeding to their physician *[see Warnings and Precautions (5.1)]*.

Instruct patients to tell their physicians and dentists that they are taking BEVYXXA, and/or any other products known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken *[see Warnings and Precautions (5.1, 5.4)]*.

Use in Patients with Severe Renal Impairment

Advise patients that the risk of bleeding is higher in people who have severe kidney problems (severe renal impairment) *[see Warnings and Precautions (5.3)]*.

Spinal/Epidural Hematoma

Advise patients having neuraxial anesthesia or spinal puncture to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel, or bladder dysfunction *[see Warnings and Precautions (5.2)]*. Instruct patients to contact their physician immediately if any of these symptoms occur.

Pregnancy and Lactation

Advise female patients to inform their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with BEVYXXA *[see Use in Specific Populations (8.1, 8.2)]*.

How to Take BEVYXXA

Instruct patients to take BEVYXXA with food, and instruct patients on what to do if a dose is missed *[see Dosage and Administration (2.2)]*.

Manufactured for:

Portola Pharmaceuticals, Inc.

South San Francisco, California 94080 USA

BTX-US-V.1.0

Exhibit C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208383

NDA APPROVAL

Portola Pharmaceuticals, Inc.
Attention: Janice Castillo
Senior Vice President, Regulatory Affairs
270 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Castillo:

Please refer to your New Drug Application (NDA) dated October 23, 2016, received October 24, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Bevyxxa® (betrixaban) capsule, 40 mg and 80 mg.

This new drug application provides for the use of Bevyxxa® (betrixaban) capsule for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

EXPIRATION DATING PERIOD

Expiration dating period of 24 months for the commercial drug product when stored under controlled room temperature conditions 20°C to 25°C (68°F to 77°F) in the commercial packaging.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, medication guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on June 20, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 208383.**" Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for betrixaban was not referred to a FDA advisory committee because this drug is not the first in its class and the evaluation of safety data when used for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE did not raise significant safety or efficacy issues that were unexpected for a drug of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to < 2 years because of the following:

- The necessary studies are impossible or highly impracticable. This is because the numbers of patients in this age group is low and the patients are geographically dispersed.

- There is evidence strongly suggesting that the drug product would be ineffective and unsafe in this pediatric group. The Netherlands pediatric working group, based on their extensive literature search, suggested that there is little evidence that primary prophylactic anticoagulation provided any benefit in neonates or infants and toddlers who have a central venous catheter (80% of VTE events in neonate occur as a complication of CVCs). In addition, given the variability of food intake that occurs in the subgroups (neonates, infants and toddlers), which have the potential to lead to a supra-therapeutic betrixaban level in fast state and consequently potential increase of major bleeding events in this subgroup.

We are deferring submission of your pediatric studies for ages 2 to < 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(C) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

PMR 3229-1 Conduct a single-dose, open label pediatric pharmacokinetic/ pharmacodynamic study in the fed state. The study population will be children two years of age or older who have just completed a course of anticoagulation for venous thrombosis.

The timetable you submitted on June 19, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/30/2016
Study Completion:	12/31/2019
Final Report Submission:	06/30/2020

PMR 3229-2 Conduct a venous thromboembolism prophylaxis study in immobilized adolescents hospitalized for acute medical or surgical disease. The study will be a single-arm, open-label study of betrixaban with point estimates of events to be compared to historical controls. The objective of this study is to identify the safety and efficacy of betrixaban in the pediatric population.

The timetable you submitted on June 19, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/31/2018
Study Completion:	05/31/2020
Final Report Submission:	12/31/2020

PMR 3229-3 Conduct a randomized multi-center, active-controlled clinical trial comparing betrixaban to standard of care (in patients two years of age or older with central venous catheter) or either enoxaparin or warfarin (in patients two years of age or older with secondary prevention indication) in prevention of venous thromboembolism. The objective of this study is to identify the safety and efficacy of betrixaban in the pediatric population.

The timetable you submitted on June 19, 2017, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/31/2018
Study Completion:	12/31/2022
Final Report Submission:	06/30/2023

Submit the protocols to your IND 72679, with a cross-reference letter to this NDA.

Reports of this/these required pediatric postmarketing studyies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Thomas Iype, Regulatory Project Manager, at (240) 402 6861.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RICHARD PAZDUR
06/23/2017

Exhibit D

US006835739B2

(12) **United States Patent**
Zhu et al.

(10) **Patent No.: US 6,835,739 B2**
(45) **Date of Patent: Dec. 28, 2004**

(54) **BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA**

(75) Inventors: **Bing-Yan Zhu**, Belmont, CA (US); **Penglie Zhang**, Foster City, CA (US); **Lingyan Wang**, East Brunswick, NJ (US); **Wenrong Huang**, Cupertino, CA (US); **Erick A. Goldman**, Berkeley, CA (US); **Wenhao Li**, South San Francisco, CA (US); **Jingmei Zuckett**, Bellevue, WA (US); **Yonghong Song**, Foster City, CA (US); **Robert M. Scarborough**, Half Moon Bay, CA (US)

(73) Assignee: **Millennium Pharmaceuticals, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/687,334**

(22) Filed: **Oct. 15, 2003**

(65) **Prior Publication Data**

US 2004/0097561 A1 May 20, 2004

Related U.S. Application Data

(63) Continuation of application No. 10/126,976, filed on Apr. 22, 2002, now abandoned, which is a continuation of application No. 09/794,225, filed on Feb. 28, 2001, now Pat. No. 6,376,515, which is a continuation-in-part of application No. 09/663,420, filed on Sep. 15, 2000.

(60) Provisional application No. 60/185,746, filed on Feb. 29, 2000.

(51) **Int. Cl.**[7] **C07D 401/02**; A61K 31/44

(52) **U.S. Cl.** **514/318**; 514/341; 514/343; 514/352; 546/193; 546/272.7; 546/276.4; 546/309

(58) **Field of Search** 514/318.341, 393, 514/352; 546/193, 272.7, 276.4, 309

(56) **References Cited**

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6,376,515	B2 *	4/2002	Zhu et al.	514/318

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WO	99/00127		1/1999
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(List continued on next page.)

Primary Examiner—Zinna Northington Davis
(74) *Attorney, Agent, or Firm*—Townsend and Townsend and Crew LLP

(57) **ABSTRACT**

Novel benzamide compounds including their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives having activity against mammalian factor Xa are described. Compositions containing such compounds are also described. The compounds and compositions are useful in vitro or in vivo for preventing or treating coagulation disorders.

11 Claims, No Drawings

OTHER PUBLICATIONS

Michael R. Wiley et al., "Structure–Based Design of Potent, Amidine–Derived Inhibitors of Factor Xa: Evaluation of Selectively, Anticoagulant Activity, and Antithrombotic Activity", *J. Med. Chem.*, vol. 43, pp. 883–899 (2000).

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W. E. Bachmann et al., "Reduction by Magnesium+Magnesium Halide, XIII. The Reaction Between Epoxy Ketones and Grignard Reagents", *Journal of the American Chemical Society*, vol. 56, No. 7, pp. 1559–1560 (1934).

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BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 10/126,976 filed Apr. 22, 2000, now abandoned which is a continuation of U.S. patent application Ser. No. 09/794,225 filed Feb. 28, 2001, now U.S. Pat. No. 6,376,515, which is a continuation-in-part of U.S. patent application Ser. No. 09/663,420 filed Sep. 15, 2000, which claims benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional Application No. 60/185,746 filed Feb. 29, 2000, each of which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel monoamidino-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

BACKGROUND OF THE INVENTION

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in Hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411–436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one

molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617–619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as in vitro diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see e.g., WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. U.S. Pat. No. 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. et al., "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162–10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., et al., "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593–596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R. R. et al., "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339–349 (1980); Turner, A. D. et al., "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry, 25, 4929–4935 (1986); Hitomi, Y. et al., "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164–168 (1985); Sturzebecher, J. et al., "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245–252 (1989); Kam, C. M. et al., "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547–2557 (1988); Hauptmann, J. et al., "Comparison of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63; 220–223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)—NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naththyl group via a straight or branched chain alkylene, —C(=O) or —$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as

restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly compounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability and/or solubility.

SUMMARY OF THE INVENTION

As discussed above, a number of non-peptide, specific, factor Xa inhibitors have been described either in the scientific or patent literature (Zhu and Scarborough, Ann. Rep. Med. Chem. 35: 83–102 (2000)). Most of these compounds rely on the interaction of P1 and P4 elements of the inhibitor compounds with the S1 and S4 sub-sites on the factor Xa enzyme. In general, it has been described that P1 elements utilize a highly charged benzamidine functionality in order to interact with the S1 pocket of the factor Xa enzyme. Furthermore, substitution on the benzamidine nitrogens either by alkylation or cyclization (cyclic amidines) of these previously described inhibitors is detrimental to their interaction with the enzyme at the S1 pocket. In the present application, a novel series of inhibitors of factor Xa which do not utilize a S1-interacting benzamidine but utilize a neutral P1 species are described. In addition the compounds also utilize a substituted benzamidine or a cyclic amidine as a P4 element which can each interact with the S4 sub-site of factor Xa enzyme. Surprisingly, the inhibitors of this invention with modified amidine elements are not only of high potency in vitro, but also have excellent pharmacological and pharmaceutical properties in vivo. These are results that would not have been predicted for such structures.

Accordingly, the present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals characterized by undesired thrombosis or which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In one embodiment, the present invention relates to a compound according to the formula (I):

A-Q-D-E-G-J-X (I)

where:

A is selected from:

(a) C_1–C_6-alkyl;

(b) C_3–C_8-cycloalkyl;

(c) —$N(R^1,R^2)$, $N(R^1,R^2)$—$C(=NR^3)$—, $N(R^1,R^2)$—$C(=NR^3)$—$N(R^4)$—, R^1—$C(=NR^3)$—, R^1—$C(=NR^3)$—$N(R^4)$—;

(d) phenyl, which is independently substituted with 0–2 R substitutuents;

(e) naphthyl, which is independently substituted with 0–2 R substitutuents;. and

(f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1–4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0–2 R substitutuents;

R is selected from:

H, halo, —CN, —CO_2R^1, —$C(=O)$—$N(R^1,R^2)$, $(CH_2)_m$—CO_2R^1, —$(CH_2)_m$—$C(=O)$—$N(R^1,R^2)$, —NO_2, —$SO_2N(R^1,R^2)$, —SO_2R^1, —$(CH_2)_mNR^1R^2$, —$(CH_2)_m$—$C(=NR^3)$—R^1, —$(CH_2)_m$—$C(=NR^3)$—$N(R^1,R^2)$, —$(CH_2)_m$—$N(R^4)$—$C(=NR^3)$—$N(R^1,R^2)$, —$(CH_2)_mNR^1$— group appended to a 3 to 6 membered heterocyclic ring containing from 1–4 heteroatoms selected from N, O and S, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8} cycloalkyl, —CF_3, —OR^2, and a 5–6 membered heterocyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_1–C_4-alkyl, —C_{1-4}alkyl-CN, —C_{2-6} alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4} alkylC_{3-8}cycloalkyl and —NO_2;

m is an integer of 0–2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, —OR^5, —$N(—R^5, —R^6)$, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8} cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4} alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6} alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4} alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3–8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, —CN—C_{1-4}alkyl, —C_{2-6} alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4} alkylC_{3-8}cycloalkyl and —NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkyl-phenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

R^5 and R^6 taken together can form a 3–8 membered cycloalkyl or a heterocyclic ring system, wherein the

heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, —C_1–C_4-alkyl, —CN—C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8} cycloalkyl and —NO_2;

Q is a member selected from the group consisting of:

a direct link, —CH_2—, —C(=O)—, —O—, —N(R^7)—, —N(R^7)CH_2—, —CH_2N(R^7)—, —C(=NR^7)—, —C(=O)—N(R^7)—, —N(R^7)—C(=O)—, —S—, —SO—, —SO_2—, —SO_2—N(R^7)— and —N(R^7)—SO_2—;

R^7 is selected from:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkyl-phenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0–2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0–2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1–4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0–2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, —NO_2, —$(CH_2)_n NR^{2a}R^{3a}$, —$(CH_2)_n CO_2R^{2a}$, —$(CH_2)_n$ $CONR^{2a}R^{3a}$, —$SO_2NR^{2a}R^{3a}$, —SO_2R^{2a}, —CF_3, —OR^{2a}, and a 5–6 membered aromatic heterocyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2,

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkyl-phenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

n is an integer of 0–2;

E is a direct link or a member selected from the group consisting of:

—C_{1-2}-alkyl-, —O—, —S—, —SO—, —SO_2—, —C_{0-1}-alkyl-C(=O), —C_{0-1}-alkyl-C(=O)—N(—R^8)—C_{0-1}-alkyl-, —C_{0-1}-alkyl-N(—R^8)—C(=O)—C_{0-1}-alkyl-, —N(—R^8)—C(=O)—N(—R^8)— and —C_{0-1}-alkyl-N(—R^8)—;

R^8 is a member selected from the group consisting of:.

H, —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-C(=O)—OH, —C_{1-4}-alkyl-C(=O)—O—C_{1-4}-alkyl, and —C_{1-4}-alkyl-C(=O)—N(—R^{2b}, —R^{3b});

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, —C_{1-4}-alkyl, —C_{0-4}-alkyl-aryl; —C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5–8 membered heterocyclic ring containing 1–4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0–2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; —C_{1-4}-alkyl; —CN, —NO_2; —C(=O)—N(—R^{2c}, R^{3c}); —C(=O)—OR^{2c}; —$(CH_2)_q$—N(—R^{2c}, —R^{3c}); —SO_2—N(—R^{2c}, —R^{3c}); —SO_2R^{2c}; —CF_3 and —$(CH_2)_q$—OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; —C_{1-4}-alkyl and —C_{1-4}-alkyl-aryl;

q is an integer of 0–2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the —C_2-alkenyl or —C_{3-8}-cycloalkenyl are substituted with 0–4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0–4 R^{1d} groups;

(c) a 3–8 membered a saturated, partially unsaturated or aromatic monocyclic-heterocyclic ring system containing 1–4 heteroatoms selected from N, O and S, wherein 0–2 ring atoms of the heterocyclic ring may be substituted with 0–4 R^{1d} groups; and,

(d) an 8–10 membered fused heterocyclic bicyclic ring system, containing 1–4 heteroatoms selected from N, O and S, wherein 0–2 ring atoms of the fused bicyclic ring system may be substituted with 0–4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, CN; —NO_2; —$(CH_2)_{0-6}$—$NR^{2d}R^{3d}$; —$SO_2NR^{2d}R^{3d}$; —SO_2R^{2d}; —CF_3; —$(CH_2)_{0-6}$—OR^{2d}; —OH, —OC_{1-6}alkyl, —O—$(CH_2)_{1-6}OR^{2d}$; —O—$(CH_2)_{1-6}$—C(=O)—O—R²d; —O—$(CH_2)_{1-6}$—C(=O)—N(R^{2d},R^3d); —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—$(CH_2)_{1-6}$—N(R^{2d},R^{3d}); —C(=O)—N(R^{2d},R^{3d}); —N(R^{5a})—$(CH_2)_{1-6}$—C(=O)—N(R^{2d},R^{3d}); —N(—$(CH_2)_{1-6}$—OR^{2d})$_2$; —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—C(=O)—R^{2d}; —N(R^{5a})—SO_2—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—O—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—N(R^{2d},R^{3d}); —$(CH_2)_{0-6}$—C(=NR^{2d})—N(R^{3d},R^{4d}); —$(CH_2)_{0-6}$—N(R^{5a})C(=NR^{2d})—N(R^{3d},R^{4d}); a —$(CH_2)_{0-6}$—N(R^{3d})C_{5-6} membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S, and a —$(CH_2)_{0-6}$-5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, —CN; —NO_2; carbocylic aryl, —CN; —NO_2; or

R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5–7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5–8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of:

—N(—R^9)—C(=O)—; —C(=O)—N(—R^9)—; —O—; —S—; —SO—; —SO_2—; —CH_2—; —N(—R^9)—; and —N(—R^9)—SO_2—;

R^9 is a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-4}-alkyl-carbocyclic aryl; —$(CH_2)_{0-4}$-5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S; —$(CH_2)_{1-6}$—C(=O)—O—C_{1-4}-alkyl; and —$(CH_2)_{1-6}$—C(=O)—N(R^{6a},R^{6b});

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

H and —C_{1-6}-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0–3 R^{1e} groups;

(b) naphthyl substituted with 0–3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1–3 N atoms and having 0–3 ring atoms substituted with 0–3 R^{1e} groups; and

(d) an 8–10 membered fused aromatic heterocyclic bicyclic ring system containing 1–4 heteroatoms selected from N, O and S and 0–3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0–3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; —C_{1-4}-alkyl; carbocyclic aryl; —C_{0-2}-alkyl-CN; —O—R^{2e}; —C_{0-2}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-C(=O)—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-NO_2; —C_{0-2}-alkyl-N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2-R^{2e}; trihaloalkyl; —O—C_{0-2}-alkyl-O—R^{2e}; —C_{0-2}-alkyl-O—R^{2e}; —O—C_{1-4}-alkyl-C(=O)—N(R^{2e}, R^{3e}); —O—C_{1-4}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-N(R^{2e})—C(=O)—R^{3e}; —C_{0-2}-alkyl-N(—R^{2e})—SO_2—R^{3e}; —CH_2—N(R^{2e})—C(=O)—R^{3e};—CH_2—N(R^{2e})—SO_2—R^{3e}; —$(CH_2)_{0-6}$—$NR^{2e}R^{3e}$; —C(=O)—N(R^{2e}, R^{3e}); —N(—$(CH_2)_{1-6}$—OR^{2e})$_2$; —N(R^{10})—$(CH_2)_{1-6}$—OR^{2e}; —N(R^{10})—C(=O)—R^{2e}; —N(R^{10})—SO_2—R^{2e}; —C(=N(R^{10}))—N(R^{2e},R^{3e}); and a —$(CH_2)_{0-6}$-5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-2}-alkyl-O—R^{1g}; —C_{0-2}-alkyl-N(—R^{1g}, —R^{2g});—C_{1-4}-alkyl-carbocyclic aryl; —C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5–8 membered heterocyclic ring-containing 1–4 heteroatoms selected from N, O and S which can be substituted with 0–2 R^{1g} groups;

R^{1g} and R^{2g} are independently a member selected from the group of:

H; halo; —C_{1-4}-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; —CN; —C(=O)—N(R^{3g})R^{4g}; —C(=O)—OR^{3g}; —NO_2; —$(CH_2)_p$—$NR^{3g}R^{4g}$; —$SO_2NR^{3g}R^{4g}$; —SO_2R^{3g}; —CF_3; and —$(CH_2)_p$ OR^{3g};

p is an integer of 0–2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; —C_{1-4}-alkyl and —C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by undesired thrombosis or disorders of the blood coagulation process in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkenyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkenyl each refer to radicals having from 2–12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure" and "C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are

not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, napthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5–7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement (s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocylic and bicyclic heterocylic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztriazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro [2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocylic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $—CH_2—$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an in vivo effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by in vitro assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

The invention provides a compound according to the formula (I):

A-Q-D-E-G-J-X (I)

where:

A is selected from:

(a) C_1–C_6-alkyl;

(b) C_3–C_8-cycloalkyl;

(c) —$N(R^1,R^2)$, $N(R^1,R^2)$—$C(=NR^3)$—, $N(R^1,R^2)$—$C(=NR^3)$—$N(R^4)$—, R^1—$C(=NR^3)$—, R^1—$C(=NR^3)$—$N(R^4)$—;

(d) phenyl, which is independently substituted with 0–2 R substitutuents;

(e) naphthyl, which is independently substituted with 0–2 R substitutuents; and

(f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1–4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0–2 R substitutuents;

R is selected from:

H, halo, —CN, —CO_2R^1, —C(=O)—$N(R^1, R^2)$, —$(CH_2)_m$—CO_2R^1, —$(CH_2)_m$—C(=O)—$N(R^1, R^2)$, —NO_2, —$SO_2N(R^1, R^2)$, —SO_2R^1, —$(CH_2)_mNR^1R^2$, —$(CH_2)_m$—$C(=NR^3)$—R^1, —$(CH_2)_m$—$C(=NR^3)$—$N(R^1,R^2)$, —$(CH_2)_m$—$N(R^4)$—$C(=NR^3)$—$N(R^1,R^2)$, —$(CH_2)_mNR^1$—C_{3-6} heterocyclics, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8} cycloalkyl, —CF_3, —OR^2, and a 5–6 membered heterocyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, CN—C_{1-4}alkyl, —C_{2-6} alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4} alkylC_{3-8}cycloalkyl and —NO_2;

m is an integer of 0–2;

R^1, R^2, R^3 and R are independently selected from the group consisting of:

H, —OR^5, —$N(—R^5, —R^6)$, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8} cycloalkyl, C_{0-4}alkylphenyl and —C_{0-4} alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a members elected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6} alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4} alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3–8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, —CN—C_{1-4}alkyl, —C_{2-6} alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4} alkylC_{3-8}cycloalkyl and —NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

R^5 and R^6 taken together can form a 3–8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a

member selected from the group consisting of halo, C_1–C_4-alkyl, —CN—C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

Q is a member selected from the group consisting of:

a direct link, —CH_2—, —C(=O)—, —O—, —N(R^7)—, —N(R^7)CH_2—, —CH_2N(R^7)—, —C(=NR^7)—, —C(=O)—N(R^7)—, —N(R^7)—C(=O)—, —S—, —SO—, —SO_2—, —SO_2—N(R^7)— and —N(R^7)—SO_2—;

R^7 is selected from:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkyl-phenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0–2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0–2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1–4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0–2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, —NO_2, —$(CH_2)_n$N$R^{2a}R^{3a}$, —$(CH_2)_n$$CO_2R^{2a}$, —$(CH_2)_n$ CON$R^{2a}R^{3a}$, —SO_2N$R^{2a}R^{3a}$, —SO_2R^{2a}, —CF_3, —OR^{2a}, and a 5–6 membered aromatic heterocyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkyl-phenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

n is an integer of 0–2;

E is a direct link or a member selected from the group consisting of:

—C_{1-2}-alkyl-, —O—, —S—, —SO—, —SO_2—, —C_{0-1}-alkyl-C(=O)—, —C_{0-1}-alkyl-C(=O)—N(—R^8)—C_{0-1}-alkyl-, —C_{0-1}-alkyl-N(—R^8)—C(=O)—C_{0-1}-alkyl-, —N(—R^8)—C(=O)—N(—R^8)— and —C_{0-1}-alkyl-N(—R^8)—;

R^8 is a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-C(=O)—OH, —C_{1-4}-alkyl-C(=O)—O—C_{1-4}-alkyl, and —C_{1-4}-alkyl-C(=O)—N(—R^{2b}, —R^{3b});

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, —C_{1-4}-alkyl, —C_{0-4}-alkyl-aryl; —C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5–8 membered heterocyclic ring containing 1–4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0–2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; —C_{1-4}-alkyl; —CN, —NO_2; —C(=O)—N(—R^{2c}, —R^{3c}; —C(=O)—OR^{2c}; —$(CH_2)_q$—N(—R^{2c}, —R^{3c}); —SO_2—N(—R^{2c}, —R^{3c}); —SO_2R^{2c}; —CF_3 and —$(CH_2)_q$—OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; —C_{1-4}-alkyl and —C_{1-4}-alkyl-aryl;

q is an integer of 0–2;

G is member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein C_2-alkenyl or C_{3-8}-cycloalkenyl are substituted with 0–4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0–4 R^{1d} groups;

(c) a 3–8 membered a saturated, partially unsaturated or aromatic monocyclic-heterocyclic ring system containing 1–4 heteroatoms selected from N, O and S, wherein 0–4 ring atoms of the heterocyclic ring may be substituted with 0–4 R^{1d} groups; and,

(d) an 8–10 membered fused heterocyclic bicyclic ring system, containing 1–4 heteroatoms selected from N, O and S, wherein 0–4 ring atoms of the fused bicyclic ring system may be substituted with 0–4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, —CN; —NO_2; —$(CH_2)_{0-6}$—N$R^{2d}R^{3d}$; —SO_2N$R^{2d}R^{3d}$; —SO_2R^{2d}; —CF_3; —$(CH_2)_{0-6}$—OR^{2d}; —OH, —OC_{1-6}alkyl, —O—$(CH_2)_{1-6}OR^{2d}$; —O—$(CH_2)_{1-6}$—C(=O)—O—R^{2d}; —O—$(CH_2)_{1-6}$—C(=O)—N(R^{2d},R^{3d}); —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—$(CH_2)_{1-6}$—N(R^{2d},R^{3d}); —C(=O)—N(R^{2d},R^{3d}); —N(R^{5a})—$(CH_2)_{1-6}$—C(=O)—N(R^{2d},R^{3d}); —N(—$(CH_2)_{1-6}$—OR^{2d})$_2$; —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—C(=O)—R^{2d}; —N(R^{5a})—SO_2—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—O—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—N(R^{2d},R^{3d}); —$(CH_2)_{0-6}$—C(=NR^{2d})—N(R^{3d},R^{4d}); —$(CH_2)_{0-6}$—N(R^{5a})C(=NR^{2d})—N(R^{3d},R^{4d}); and —$(CH_2)_{0-6}$—N(—R^{3d})— group attached directly by its nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S, and a —$(CH_2)_{0-6}$— group attached to a 5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, —CN; —NO_2; carbocylic aryl, —CN; —NO_2; or

R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5–7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5–8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of:

—N(—R^9)—C(=O)—; —C(=O)—N(—R^9)—; —O—; —S—; —SO—; —SO_2—; —CH_2—; —N(—R^9)—; and —N(—R^9)—SO_2—;

R^9 is a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-4}-alkyl-carbocyclic aryl; —$(CH_2)_{0-4}$-5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S; —$(CH_2)_{1-6}$—C(=O)—O—C_{1-4}-alkyl; and —$(CH_2)_{1-6}$—C(=O)—N(R^{6a},R^{6b});

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

H and —C_{1-6}-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0–3 R^{1e} groups;

(b) naphthyl substituted with 0–3 R^{1e} groups;

(c) a 6-membered aromatic heterocyclic ring system containing 1–3 N atoms and having 0–3 ring atoms substituted with 0–3 R^{1e} groups; and

(d) an 8–10 membered fused aromatic heterocyclic bicyclic ring system containing 1–4 heteroatoms selected from N, O and S and 0–3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0–3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; —C_{1-4}-alkyl; carbocyclic aryl; —C_{0-2}-alkyl-CN; —O—R^{2e}; —C_{0-2}alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-C(=O)—N(R^{2e},R^{3e}); —C_{0-2}-alkyl-NO_2; —C_{0-2}-alkyl-N(R^{2e},R^{3e}); —C_{0-2}-alkyl-SO_2—N(R^{2e},R^{3e}); —C_{0-2}-alkyl-SO_2—R^{2e}; trihaloalkyl; —O—C_{0-2}-alkyl-O—R^{2e}; —C_{0-2}-alkyl-O—R^{2e}; —O—C_{1-4}-alkyl-C(=O)—N(R^{2e},R^{3e}); —O—C_{1-4}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-N(R^{2e})—C(=O)—R^{3e}; —C_{0-2}-alkyl-N(—R^{2e})—SO_2—R^{3e}; —CH_2—N(R^{2e})—C(=O)—R^{3e}; —CH_2—N(R^{2e})—SO_2—R^{3e}; —$(CH_2)_{0-6}$—N$R^{2e}R^{3e}$; —C(=O)—N(R^{2e},R^{3e}); —N(—$(CH_2)_{1-6}$—OR^{2e})$_2$; —N(R^{10})—$(CH_2)_{1-6}$—OR^{2e}; —N(R^{10})—C(=O)—R^{2e}; —N(R^{10})—SO_2—R^{2e}; —C(=N(R^{10}))—N(R^{2e},R^{3e}); and a —$(CH_2)_{0-6}$-5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-2}-alkyl-O—R^{1g}; —C_{0-2}-alkyl-N(—R^{1g}, —R^{2g});—C_{1-4}alkyl-carbocyclic aryl; —C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to Which they are attached can form 5–8 membered heterocyclic ring containing 1–4 heteroatoms selected from N, O and S which can be substituted with 0–2 R^{1g} groups;

R^{1g} and R^{2g} are independently a member selected from the group of:

H; halo; —C_{1-4}-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; —CN; —C(=O)—N(R^{3g})R^{4g}; —C(=O)—OR^{3g}; —NO_2; —$(CH_2)_p$—N$R^{3g}R^{4g}$; —SO_2N$R^{3g}R^{4g}$; —SO_2R^{3g}; —CF_3; and —$(CH_2)_p$OR^{3g};

p is an integer of 0–2; and

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and —C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

A preferred embodiment of formula I are compounds of formula (Ia):

A-Q-D-E-G-J-X (Ia)

where:

A is selected from:

(a) C_1–C_6-alkyl;

(b) C_3–C_8-cycloalkyl;

(c) —N(R^1,R^2), N(R^1,R^2)—C(=NR^3)—, N(R^1,R^2)—C(=NR^3)—N(R^4)—, R^1—C(=NR^3)—, R^1—C(=NR^3)—N(R^4)—;

(d) phenyl, which is independently substituted with 0–2 R substitutuents;

(e) naphthyl, which is independently substituted with 0–2 R substitutuents; and

(f) monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1–4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0–2 R substitutuents;

R is selected from:

H, halo, —CN, —CO_2R^1, —C(=O)—N(R^1, R^2), —$(CH_2)_m$—CO_2R^1, —$(CH_2)_m$—C(=O)—N(R^1, R^2), —NO_2, —SO_2N(R^1, R^2), —SO_2R^1, —$(CH_2)_m$NR^1R^2, —$(CH_2)_m$—C(=NR^3)—R^1, —$(CH_2)_m$—C(=NR^3)—N(R^1,R^2), —$(CH_2)_m$—N(R^4)—C(=NR^3)—N(R^1, R^2), —$(CH_2)_m$NR^1— group attached to a 3–6 membered heterocyclic ring having from 1 to 3 heteroatoms selected from the group consisting of N, O and S, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CF_3, —OR^2, and a 5–6 membered heterocyclic aromatic or partially saturated system, including imidazoline, containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -methyl, —C_2–C_4-alkyl, —CN, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

m is an integer of 0–2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, —OR, —N(—R^5, —R^6), —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

R^1 and R^2, or R^3 and R^4 taken together can form a 3–8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently

replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, —CN—C_{1-4}alkyl, —C_{2-6} alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4} alkylC_{3-8}cycloalkyl and —NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

R^5 and R^6 taken together can form a 3–8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, —CN—C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

Q is a member selected from the group consisting of:

a direct link, —CH_2—, —C(=O)—, —O—, —NH—, —NMe—, —$NHCH_2$—, —$NMeCH_2$—, —CH_2NH—, —C(=NH)—, —C(=O)-NH—, —NH—C(=O)—, —CH_2NMe—, —C(=NMe)—;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0–2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0–2 R^{1a} substitutuents; and

a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1–4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0–2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, —NO_2, —$(CH_2)_nNR^{2a}R^{3a}$, —$(CH_2)_nCO_2R^{2a}$, —$(CH_2)_n$ $CONR^{2a}R^{3a}$, —$SO_2NR^{2a}R^{3a}$, —SO_2R^{2a}, —CF_3, —OR^{2a}, and a 5–6 membered aromatic heterocyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylphenyl and —C_{0-4}alkylnaphthyl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

n is an integer of 0–2;

E is a member selected from the group consisting of:

a direct link, —O—, —NH—, —CH_2NH—, —$NHCH_2$—, —NMe—, —NH—C(=O)—NH—, —C(=O)—NH—, —NH—C(=O)—;

G is a member selected from the group consisting of:

(a) a C_2-alkenyl group or a C_{3-8}-cycloalkenyl group, wherein the alkenyl group and cycloalkenyl group attachment points are the alkenyl carbon atoms and wherein the C_2-alkenyl group or C_{3-8}-cycloalkenyl group is substituted with 0–4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0–4 R^{1d} groups;

(c) a 3–8 membered a saturated, partially unsaturated or aromatic monocyclic-heterocyclic ring system containing 1–4 heteroatoms selected from N, O and S, wherein 0–4 ring atoms of the heterocyclic ring may be substituted with 0–4 R^{1d} groups; and,

(d) an 8–10 membered fused heterocyclic bicyclic ring system, containing 1–4 heteroatoms selected from N, O and S, wherein 0–4 ring atoms of the fused bicyclic ring system may be substituted with 0–4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, —CN; —NO_2; —$(CH_2)_{0-6}$—$NR^{2d}R^{3d}$; —$SO_2NR^{2d}R^{3d}$; —SO_2R^{2d}; —CF_3; —$(CH_2)_{0-6}$—OR^{2d}; —OH, —OC_{1-6}alkyl, —O—$(CH_2)_{1-6}OR^{2d}$; —O—$(CH_2)_{1-6}$—C(=O)—O—R^{2d}; —O—$(CH_2)_{1-6}$—C(=O)—$N(R^{2d},R^{3d})$; —$N(R^{5a})$—$(CH_2)_{1-6}$—OR^{2d}; —$N(R^{5a})$—$(CH_2)_{1-6}$—N (R^{2d},R^{3d}); —C(=O)—$N(R^{2d},R^{3d})$; —$N(R^{5a})$— $(CH_2)_{1-6}$—C(=O)—$N(R^{2d},R^{3d})$; —N(—$(CH_2)_{1-6}$— $OR^{2d})_2$; —$N(R^{5a})$—$(CH_2)_{1-6}$—OR^{2d}; —$N(R^{5a})$—C (=O)—R^{2d}; —$N(R^{5a})$—SO_2—R^{2d}; —$(CH_2)_{0-6}$—C (=O)—O—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—$N(R^{2d},R^{3d})$; —$(CH_2)_{0-6}$—C(=NR^{2d})—$N(R^{3d},R^{4d})$; —$(CH_2)_{0-6}$— $N(R^{5a})C(NR^{2d})$—$N(R^{3d},R^{4d})$; and a —$(CH_2)_{0-6}$—N (R^{3d}) group witch is attached via the nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S, and a —$(CH_2)_{0-6}$— group attached to a 5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, —CN; —NO_2; carbocylic aryl, —CN; —NO_2; or

R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5–7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5–8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

J is a member selected from the group consisting of:

a direct link, —O—, —NH—, —NMe—, —C(=O)—NH—, —NH—C(=O)—;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0–3 R^{1e} groups;

(b) naphthyl substituted with 0–3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1–3 N atoms and having 0–3 ring atoms substituted with 0–3 R^{1e} groups; and

(d) an 8–10 membered fused aromatic heterocyclic bicyclic ring system containing 1–4 heteroatoms selected from N, O and S and 0–3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0–3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; —C_{1-4}-alkyl; carbocyclic aryl; —C_{0-2}-alkyl-CN; —O—R^{2e}; —C_{0-2}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-C(=O)—N(R^{2e},R^{3e}); —C_{0-2}-alkyl-NO_2; —C_{0-2}-alkyl-N(R^{2e},R^{3e}); —C_{0-2}-alkyl-SO_2—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—R^{2e}; trihaloalkyl; —O—C_{0-2}-alkyl-O—R^{2e}; —C_{0-2}-alkyl-O—R^{2e}; —O—C_{1-4}-alkyl-C(=O)—N(R^{2e},R^{3e}); —O—C_{1-4}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-N(R^{2e})—C(=O)—R^{3e}; —C_{0-2}-alkyl-N(—R^{2e})—SO_2—R^{3e}; —CH_2—N(R^{2e})—C(=O)—R^{3e}; —CH_2—N(R^{2e})—SO_2—R^{3e}; —$(CH_2)_{0-6}$—N$R^{2e}R^{3e}$; —C(=O)—N(R^{2e},R^{3e}); —N(—$(CH_2)_{1-6}$—OR^{2e})$_2$; —N(R^{10})—$(CH_2)_{1-6}$—OR^{2e}; —N(R^{10})—C(=O)—R^{2e}; —N(R^{10})—SO_2—R^{2e}; —C(=N(R^{10}))—N(R^{2e},R^{3e}); and a —$(CH_2)_{0-6}$-5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-2}-alkyl-O—R^{1g};—C_{0-2}-alkyl-N(—R^{1g}, —R^{2g});—C_{1-4}-alkyl-carbocyclic aryl; —C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5–8 membered heterocyclic ring containing 1–4 heteroatoms selected from N, O and S which can be substituted with 0–2 R^{1g} groups;

R^{1g} and R^{2g} are independently a member selected from the group of:

H; halo; —C_{1-4}-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; —CN; —C(=O)—N(R^{3g},R^{4g}); —C(=O)—OR^{3g}; —NO_2; —$(CH_2)_p$—N$R^{3g}R^{4g}$; —SO_2N$R^{3g}R^{4g}$; —SO_2R^{3g}, —CF_3; and —$(CH_2)_p$OR^{3g};

p is an integer of 0–2; and

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and —C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment of formula I are compounds of formula (Ib):

A-Q-D-E-G-J-X (Ib)

where:

A is selected from:

(a) C_3–C_6-alkyl;

(b) C_3–C_8-cycloalkyl;

(c) —N(R^1,R^2), N(R^1,R^2)—C(=NR^3)—, N(R^1,R^2)—C(=NR^3)—N(R^4)—, R^1—C(=NR^3)—, R^1—C(=NR^3)—N(R^4)—;

(d) phenyl, which is independently substituted with 0–2 R substitutuents;

(e) naphthyl, which is independently substituted with 0–2 R substitutuents;

(f) a monocyclic or fused bicyclic ring system having from 5 to 10 ring atoms, wherein 1–4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0–2 R substitutuents;

R is selected from:

H, halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CF_3, —CN, —$(CH_2)_m$—CO_2R^1, —$(CH_2)_m$—C(=O)—N(R^1, R^2), —$(CH_2)_m$—C(=S)—N(R^1, R^2), —NO_2, —$(CH_2)_m$—SO_2N(R^1, R^2), —$(CH_2)_m$—SO_2R^1, —$(CH_2)_m$NR^1R^2, —$(CH_2)_m$OR^1, —$(CH_2)_m$—C(=NR^3)—R^1, —$(CH_2)_m$—C(=NR^3)—N(R^1,R^2), —$(CH_2)_m$—N(R^4)—C(=NR^3)—N(R^1,R^2), and a 3–8 membered cyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, —CN—C_{1-4} alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

m is an integer of 0–2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, —$(CH_2)_{0-4}OR^5$, —$(CH_2)_{0-4}$—CO_2R^5, —$(CH_2)_{0-4}$N(—R^5, —R^6), —C_{1-4}-alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylaryl and —C_{0-4}alkylheteroaryl, and a 3–8 membered cyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, —CN—C_{1-4} alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3–8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1–4 heteroatoms selected from N, O and S, where the hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, —CN, —CO_2R^5, —OH, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylaryl and —C_{0-4}alkylheteroaryl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, and —NO_2; or

R^5 and R^6 taken together can form a 3–8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, —C_1–C_4-alkyl, —CN—C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8} cycloalkyl and —NO_2;

Q is a member selected from the group consisting of:

a direct link, —CH_2—, —C(=O)—, —O—, —N(R^7)—, —N(R^7)CH_2—, —CH_2N(R^7)—, —C(=NR^7)—,

—C(=O)—N(R^7)—, —N(R^7)—C(=O)—, —S—, —SO—, —SO_2—, —SO_2—N(R^7)— and —N(R^7)—SO_2—; preferably, Q is a member selected from the group consisting of: a direct link, —CH_2—, —C(=O)—, —O—, —NH—, —NMe—, —$NHCH_2$—, —$NMeCH_2$—, —CH_2NH—, —C(=NH)—, —C(=O)—NH—, —NH—C(=O)—, —CH_2NMe—, —C(=NMe)—;

R^7 is selected from:

H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-O—C_{1-4}-alkyl, —C_{1-4}-alkyl-N(—C_{1-4}-alkyl, —C_{1-4}-alkyl); —C_{1-4}-alkyl-C(=O)—O—C_{1-4}-alkyl, and —C_{1-4}-alkyl-C(=O)—N(—C_{1-4}-alkyl, —C_{1-4}-alkyl);

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0–2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0–2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1–4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0–2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN, —NO_2, —$(CH_2)_nOR^{2a}$, —$(CH_2)_nNR^{2a}R^{3a}$, —$(CH_2)_nCO_2R^{2a}$, —$(CH_2)_nCONR^{2a}R^{3a}$, —$SO_2NR^{2a}R^{3a}$, —SO_2R^{2a}, —CF_3, and a 5–6 membered aromatic heterocyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2.

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8} cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —C_{0-4}alkylaryl and —C_{0-4}alkylheteroaryl, wherein from 1–4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, —C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6}alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl, —CN and —NO_2;

n is an integer of 0–2;

E is a direct link or a member selected from the group consisting of:

—C_{1-2}-alkyl-, —S—, —SO—, —SO_2—, —O—C_{0-1}-alkyl—, —C_{0-1}-alkyl-O—, —C_{0-1}-alkyl-N(—R^8)—, —N(—R^8)—C_{0-1}-alkyl-, —C_{0-1}-alkyl-C(=O)—N(—R^8)—C_{0-1}-alkyl, —C_{0-1}-alkyl-N(—R^8)—C(=O)—C_{0-1}-alkyl-, and —C_{0-1}-alkyl-N(—R^8)—C(=O)—N(—R^8)—C_{0-1}-alkyl-; preferably, E is a member selected from the group consisting of: a direct link, —O—, —NH—, —CH_2NH—, —$NHCH_2$—, —CH_2O—, —OCH_2—, —NMe—, —NH—C(=O)—NH—, —CH_2—NH—C(=O)—NH—, —C(=O)—NH—, —NH—C(=O)—; —C(=O)—NMe—, —NMe—C(=O)—;

R^8 is a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-OR^{2b}, —C_{1-4}-alkyl-N(—R^{2b}, —R^{3b}); —C_{1-4}-alkyl-C(=O)—OR^{2b}; —C_{1-4}-alkyl-C(=O)—N(—R^{2b}, —R^{3b}); —C_{0-4}-alkyl-C(=O)—R^{2b}; and —C_{0-4}-alkyl-SO_2—R^{2b};

R^{2b} and R^3b are each a member independently selected from the group consisting of:

H, —C_{1-4}-alkyl, —C_{1-4}-alkyl-CO_2—C_{0-4}-alkyl, —C_{0-4}-alkyl-aryl; —C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5–8 membered heterocyclic ring containing 1–4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0–2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; —C_{1-4}-alkyl; —CN, —NO_2; —C(=O)—N(—R^{2c}, —R^{3c}); —C(=O)—OR^{2c}; —$(CH_2)_q$—N(—R^{2c}, —R^{3c}); —SO_2—N(—R^{2c}, —R^{3c}); —SO_2R^{2c}; —CF_3 and —$(CH_2)_q$—OR^{2c};

R^{2c} and R_{3c} are each independently a member selected from the group consisting of:

H; —C_{1-4}-alkyl and —C_{1-4}-alkyl-aryl;

q is an integer of 0–2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the —C_2-alkenyl or —C_{3-8}-cycloalkenyl are substituted with 0–4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0–4 R^{1d} groups;

(c) a 3–8 membered a saturated, partially unsaturated or aromatic monocyclic ring system containing 1–4 heteroatoms selected from N, O and S, wherein 0–2 ring atoms of the heterocyclic ring may be substituted with 0–4 R^{1d} groups; and,

(d) an 8–10 membered fused cyclic system, containing 0–4 heteroatoms selected from N, O and S, wherein 0–2 ring atoms of the fused bicyclic ring system may be substituted with 0–4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; —CF_3; —OCF_3, —OCF_2H, —$OCFH_2$, —OCH_2CF_3, —OCF_2CF_3, C_{1-6}-alkyl, carbocylic aryl, —CN; —NO_2; —$(CH_2)_{0-6}$—$NR^{2d}R^{3d}$; —$(CH_2)_{0-6}$—OR^{2d}; —OH, —OC_{1-6}alkyl, —O—$(CH_2)_{1-6}OR^{2d}$; —O—$(CH_2)_{1-6}$—$NR^{2d}R^{3d}$; —N(R^{5a})—$(CH_2)_{1-6}$—OR^{2d}; —N(R^{5a})—$(CH_2)_{1-6}$—N(R^{2d},R^{3d}); —$(CH_2)_{0-6}$—C(=O)—O—R^{2d}; —$(CH_2)_{0-6}$—C(=O)—N(R^{2d},R^{3d}); —O—$(CH_2)_{1-6}$—C(=O)—O—R^{2d}; —O—$(CH_2)_{1-6}$—C(=O)—N(R^{2d},R^{3d}); —N(R^{5a})—$(CH_2)_{1-6}$—C(=O)—O—R^{2d}; —N(R^{5a})—$(CH_2)_{1-6}$—C(=O)—N(R^{2d},R^{3d}); —N(—$(CH_2)_{1-6}$—OR^{2d})$_2$; —N(—$(CH_2)_{1-6}$—N(R^{2d},R^{3d}))$_2$; —$(CH_2)_{0-6}$—$SO_2NR^{2d}R^{3d}$; —$(CH_2)_{0-6}$—SO_2R^{2d}; —$(CH_2)_{0-6}$—N(R^{5a})—C(=O)—R^{2d}; —$(CH_2)_{0-6}$—N(R^{5a})—SO_2—R^{2d}, —$(CH_2)_{0-6}$—C(=NR^{2d})—N(R^{3d},R^{4d}); —$(CH_2)_{0-6}$—N(R^{5a})C(=NR^{2d})—N(R^{3d},R^{4d}); —$(CH_2)_{0-6}$—N(R^{5a})C(=NR^{2d})—R^{4d}; —O—$(CH_2)_{1-6}$—$SO_2NR^{2d}R^{3d}$; —O—$(CH_2)_{1-6}$—SO_2R^{2d}; —O—$(CH_2)_{1-6}$—N(R^{5a})—C(=O)—R^{2d}; —O—$(CH_2)_{1-6}$—N(R^{5a})—SO_2—R^{2d}, —O—$(CH_2)_{1-6}$—C(=NR^{2d})—N(R^{3d},R^{4d}); —O—$(CH_2)_{1-6}$—N(R^{5a})C(=NR^{2d})—N(R^{3d},R^{4d}); —O—$(CH_2)_{1-6}$—N(R^{5a})C(=NR^{2d})—R^{4d}; —N(R^{5d})—$(CH_2)_{1-6}$—$SO_2NR^{2d}R^{3d}$; —N(R^{5d})—$(CH_2)_{1-6}$—SO_2R^{2d}; —N(R^{5d})—$(CH_2)_{1-6}$—N(R^{5a})—C(=O)—R^{2d}; —N(R^{5d})—$(CH_2)_{1-6}$—N(R^{5a})—SO_2—R^{2d}, —N(R^{5d})—$(CH_2)_{1-6}$—C(=NR^{2d})—N(R^{3d},R^{4d}); —N(R^{5d})—$(CH_2)_{1-6}$—N(R^{5a})C(=NR^{2d})—N(R^{3d},

R^{4d}); —$N(R^{5d})$—$(CH_2)_{1-6}$—$N(R^{5a})C(=NR^{2d})$—R^{4d}; and a 3–8 membered cyclic system containing from 1–4 heteroatoms selected from N, O and S, wherein from 1–4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1–C_4-alkyl, —CN—C_{1-4}alkyl, —C_{2-6}alkenyl, —C_{2-6} alkynyl, —C_{3-8}cycloalkyl, —C_{0-4}alkylC_{3-8}cycloalkyl and —NO_2;

R^{5a}, R^{2d}, R^{3d}, R^{4d} and R^{5d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, —CN; —NO_2; or

R^{2d} and R^{3d}, or R^{3d} and R^{4d} taken together with the N atoms they are independently attached form a 3–8 membered saturated, partially unsaturated or aromatic heterocyclic ring;

J is a direct link or is a member selected from the group consisting of:

—N(—R^9)—C(=O)—; —C(=O)—N(—R^9)—; —O—; —S—; —SO—; —SO_2—; —SO2N(R9)—, —CH_2—; —N(—R^9)—; and —N(—R^9)—SO_2—; preferably, J is a member selected from the group consisting of: a direct link, —O—, —SO2—, —SO2NH—, —NH—, —NMe—, —C(=O)—NH—, —NH—C(=O)—;

R^9 is a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-4}-alkylaryl; —C_{0-4}-alkyl-heteroaryl; —C_{1-4}-alkyl-OR^{6a}, —C_{1-4}-alkyl-N(—R^{6a}, —R^{6b}); —C_{1-4}-alkyl-C(=O)—OR^{6a}, and —C_{1-4}-alkyl-C(=O)—N(—R^{6a}, —R^{6b});

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

H and · C_{1-6}-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0–3 R^{1e} groups;

(b) naphthyl substituted with 0–3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1–3 N atoms and having 0–3 ring atoms substituted with 0–3 R^{1e} groups; and

(d) an 8–10 membered fused bicyclic ring system containing 1–4 heteroatoms selected from N, O and S and 0–3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0–3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; —C_{1-4}-alkyl; carbocyclic aryl; —C_{0-2}-alkyl-CN; —O—R^{2e}; —C_{0-2}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-C(=O)—N(R^{2e},R^{3e}); —C_{0-2}-alkyl-NO_2; —C_{0-2}-alkyl-N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—N(R^{2e}, R^{3e}); —C_{0-2}-alkyl-SO_2—R^{2e}; trihaloalkyl; —O—C_{0-2}-alkyl-O—R^{2e}; —C_{0-2}-alkyl-O—R^{2e}; —O—C_{1-4}-alkyl-C(=O)—N(R^{2c}, R^{3e}); —O—C_{1-4}-alkyl-C(=O)—O—R^{2e}; —C_{0-2}-alkyl-N(R^2)—C(=O)—R^{3e}; —C_{0-2}-alkyl-N(—R^{2e})—SO_2—R^{3e}; —CH_2—N(R^{2c})—C(=O)—R^{3e}; —CH_2—N(R^{2e})—SO_2—R^{3e}; —$(CH_2)_{0-6}$—$NR^{2e}R^{3e}$; —C(=O)—N(R^{2e},R^{3c}); —N(—$(CH_2)_{1-6}$—OR^{2e})$_2$; —N(R^{10})—$(CH_2)_{1-6}$—OR^{2e}; —N(R^{10})—C(=O)—R^{2e}; —N(R^{10})—SO_2—R^{2e}; —C(=N(R^{10}))—N(R^{2e},R^{3e}); and a —$(CH_2)_{0-6}$-5–6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1–4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; —C_{1-4}-alkyl; —C_{0-2}-alkyl-O—R^{1g}; —C_{0-2}-alkyl-N(—R^{1g}, —R^{2g}); —C_{1-4}-alkyl-carbocyclic aryl; —C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5–8 membered heterocyclic ring containing 1–4 heteroatoms selected from N, O and S which can be substituted with 0–2 R^{1g} groups;

R^{1g} and R^{2g} are independently a member selected from the group of:

H; halo; —C_{1-4}-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; —CN; —C(=O)—N(R^{3g})R^{4g}; —C(=O)—OR^{3g}; —NO_2; —$(CH_2)_p$—$NR^{3g}R^{4g}$; —$SO_2NR^{3g}R^{4g}$; —SO_2R^{3g}; —CF_3; and —$(CH_2)_p$ OR^{3g};

p is an integer of 0–2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and —C_{0-4}-alkyl-carbocyclic aryl;

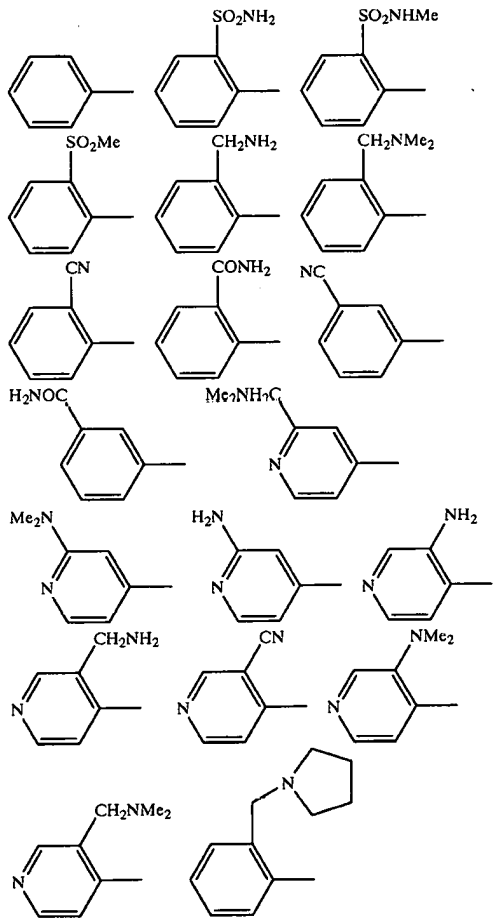
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment of formula I are compounds of formula (Ic):

A-Q-D-E-G-J-X (Ic)

where:

A is a member selected from the group consisting of:



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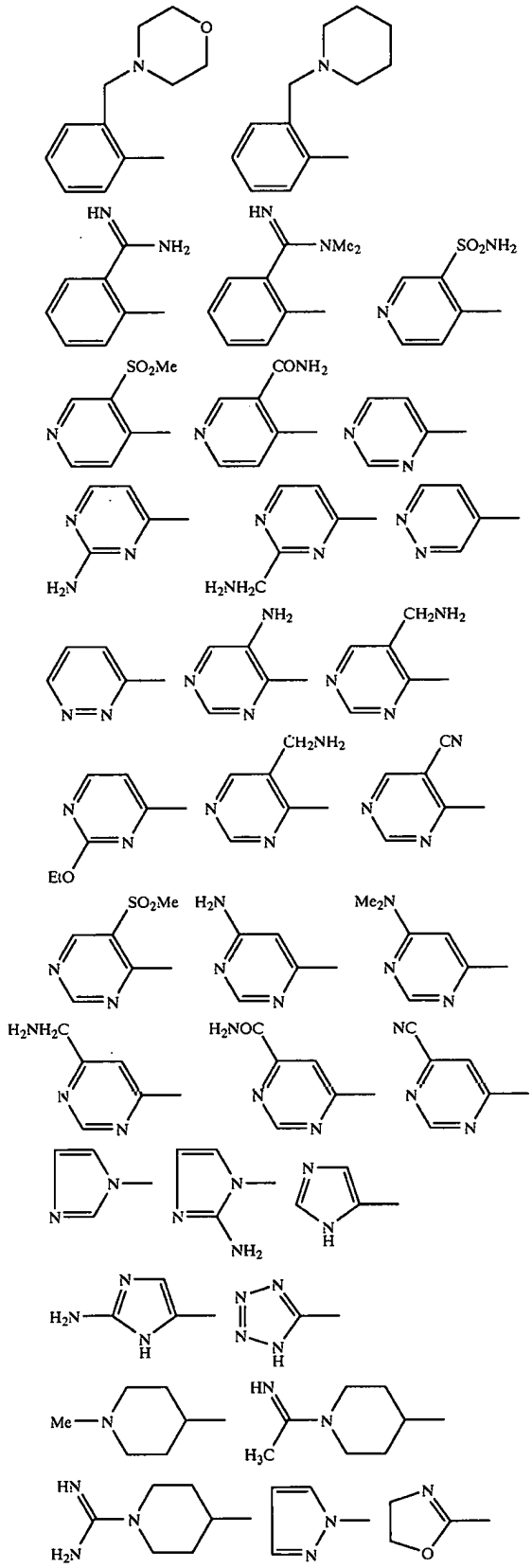

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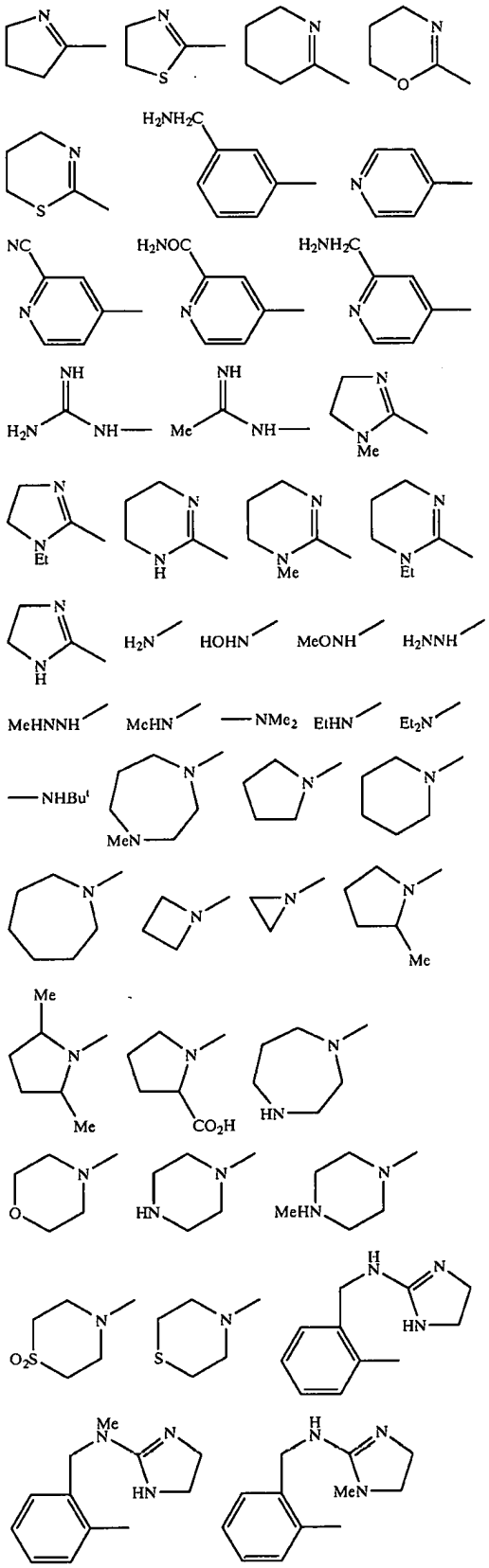

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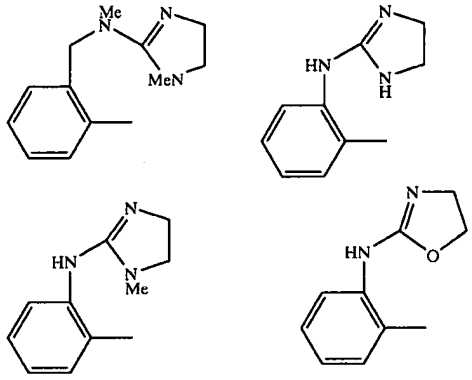
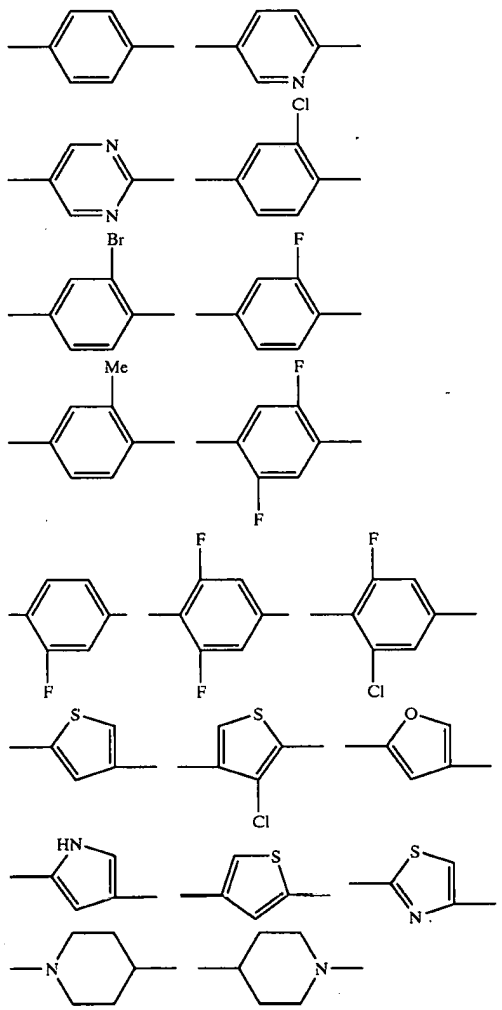


Q is a member selected from the group consisting of:

a direct link, —C(=O)—, —NH—, —NMe—, —NHCH$_2$—, —NMeCH$_2$—, —C(=NH)—, —C(=NMe)—;

D is a direct link or is a member selected from the group consisting of:



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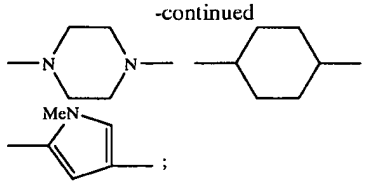
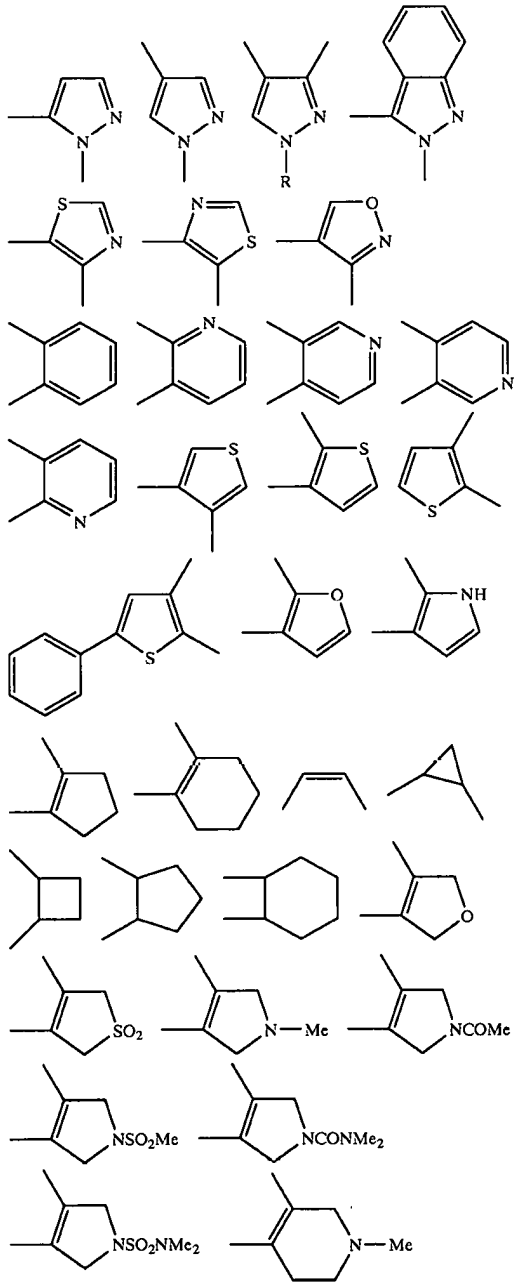


E is a member selected from the group consisting of:

a direct link, —CH$_2$NH—, —C(=O)—NH—, —NH—C(=O)—;

G is a member selected from the group consisting of:



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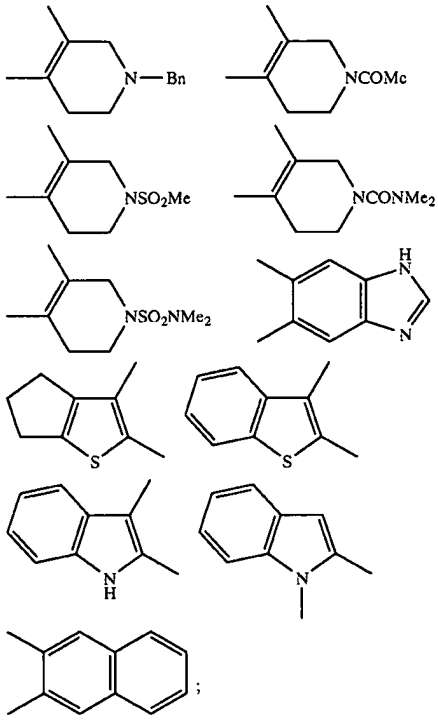
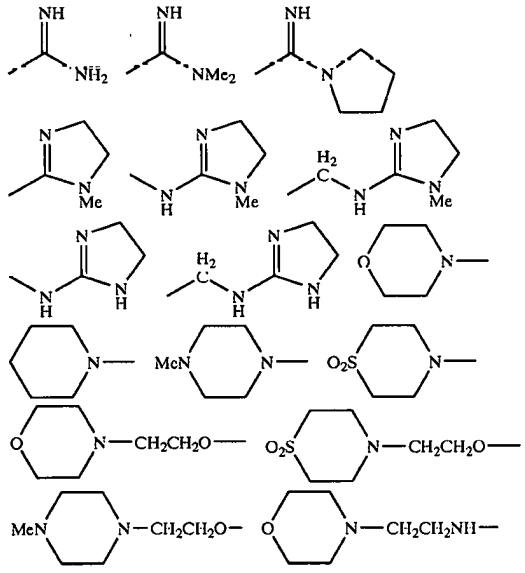


;

G is substituted by 0–4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

H, $-CH_3$, $-CF_3$, —Cl, —F, —Br, $-NH_2$, $-NMe_2$, —OH, —OMe, $-NHSO_2Me$, $-NO_2$, —CN, —C(=O)—OMe, $-CO_2H$, $-CONH_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-NHC(=O)Me$, $-C(=O)N(-Me)_2$, $-CH_2NH_2$, $-CH_2N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2C(=O)-OMe$, $-OCH_2C(=O)-NH$, and $-OCH_2C(=O)N(-Me)_2$.



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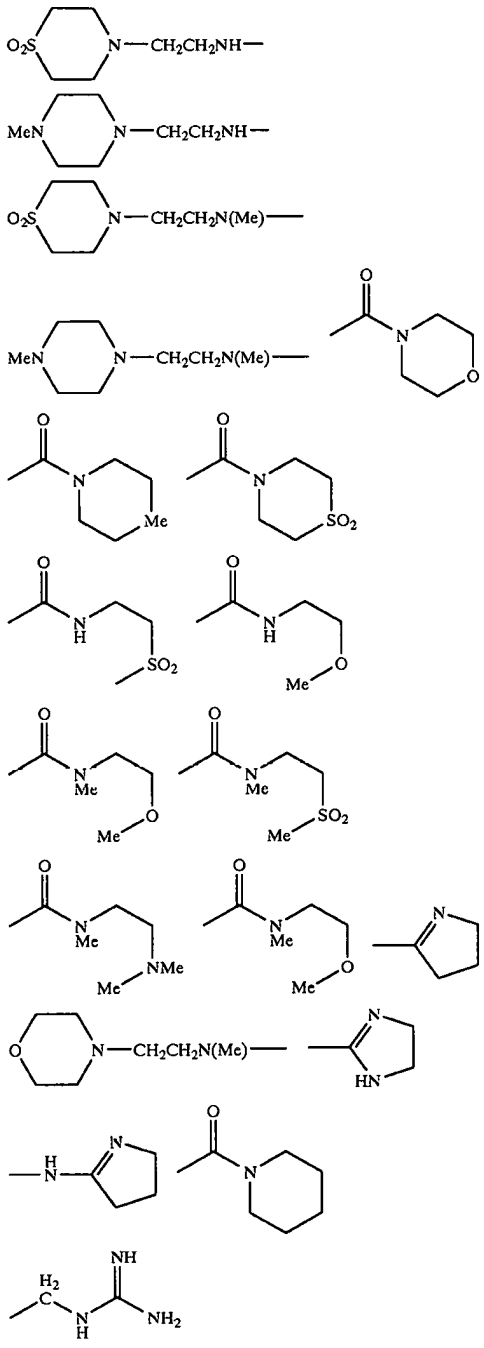
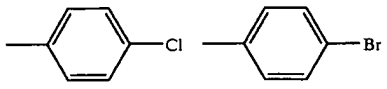


J is a member selected from the group consisting of:

a direct link, —O—, —NH—, —C(=O)—NH— and —NH—C(=O)—;

X is a member selected from the group consisting of:



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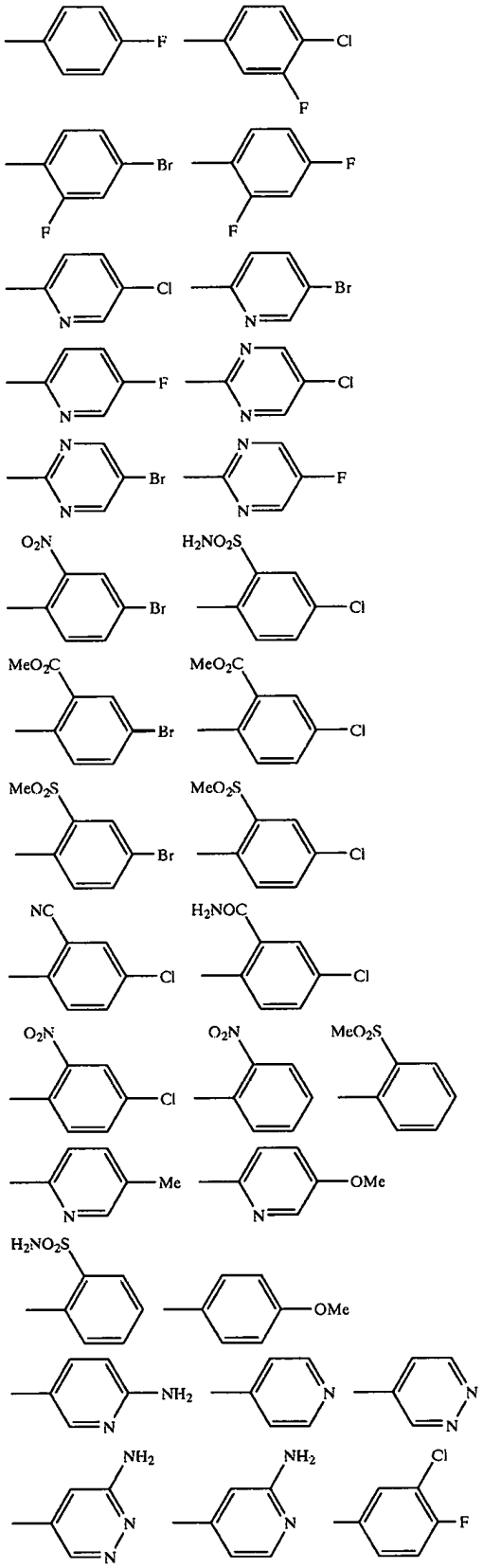

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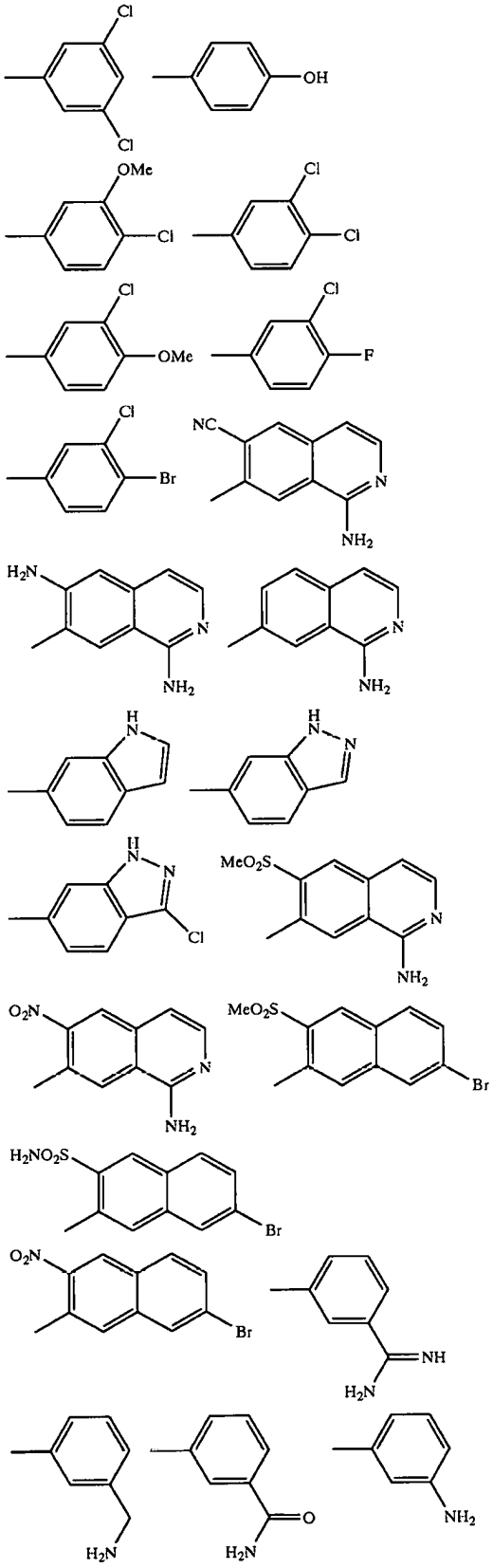

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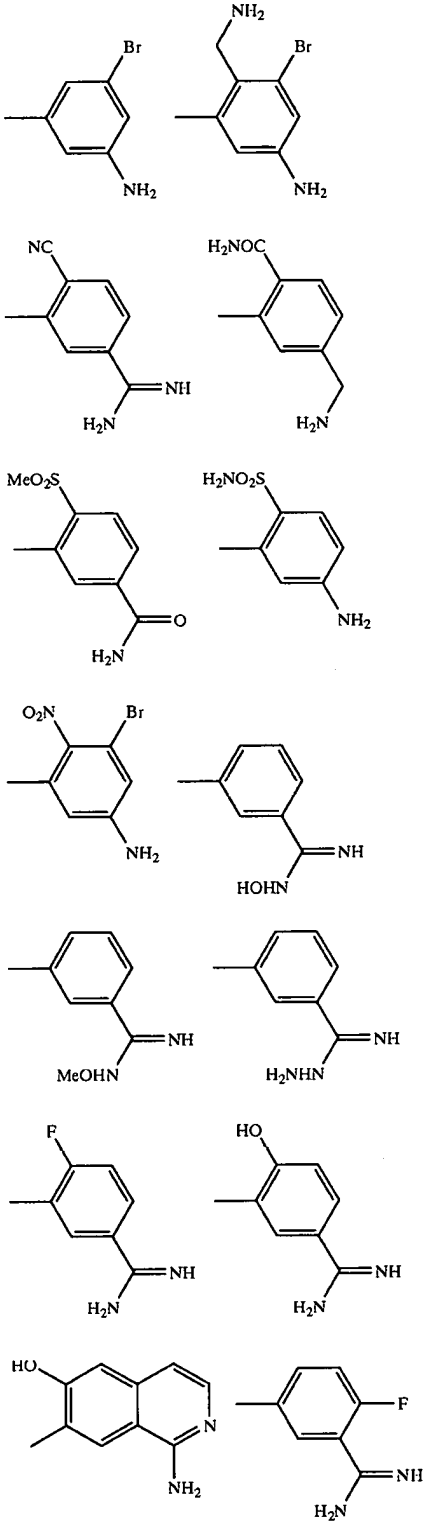
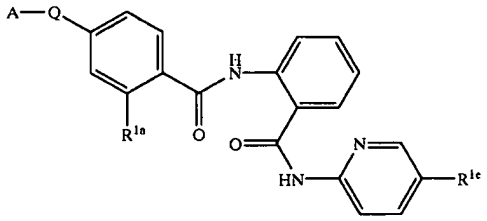


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Still another preferred embodiment of the invention are compounds of the following formula (II):



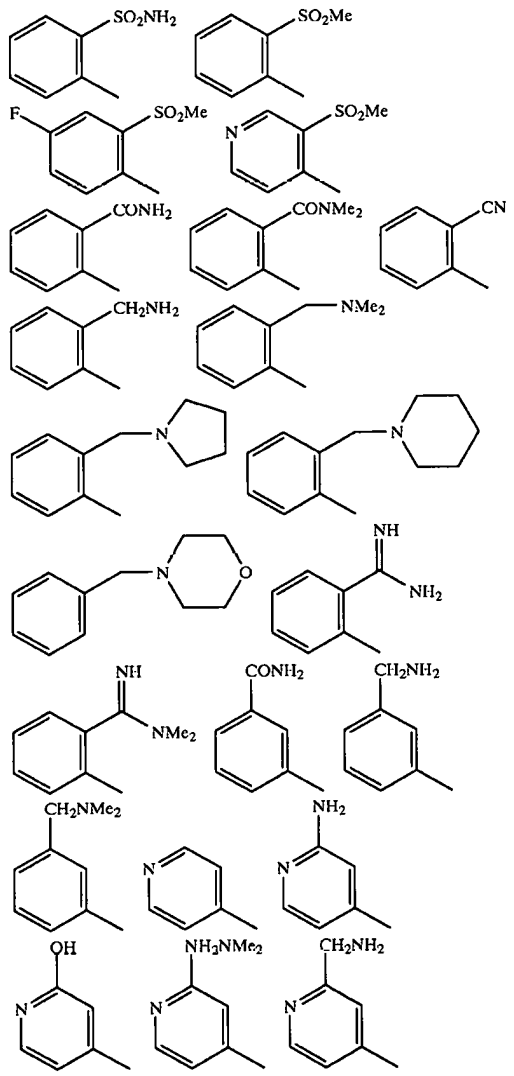
(II)

where:

R^{1a} is a member selected from the group consisting of: H, —F, —Cl and —Br;

R^{1e} is a member selected from the group consisting of: H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; and

A-Q is a member selected from the group consisting of:



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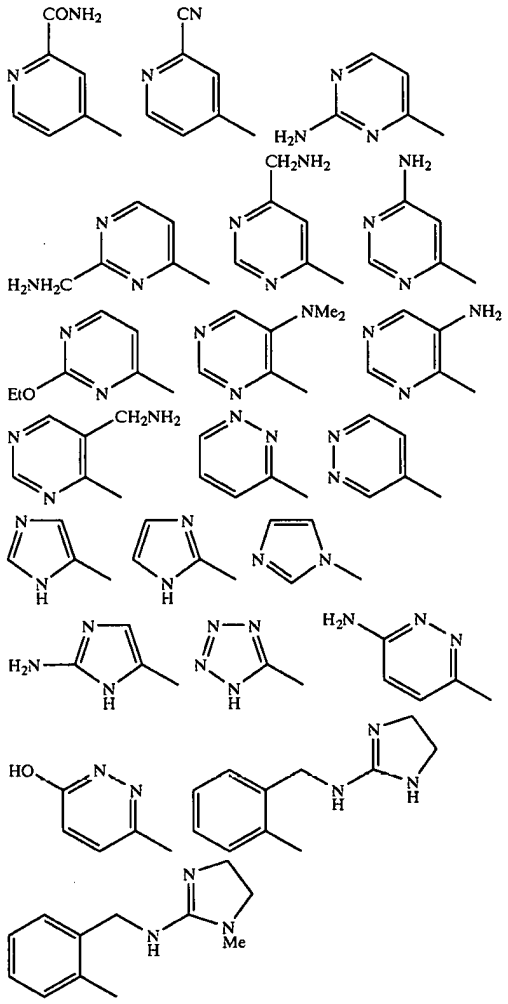
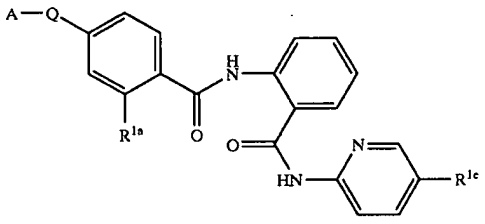


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Still another preferred embodiment the invention are compounds of formula (III):

(III)



where:

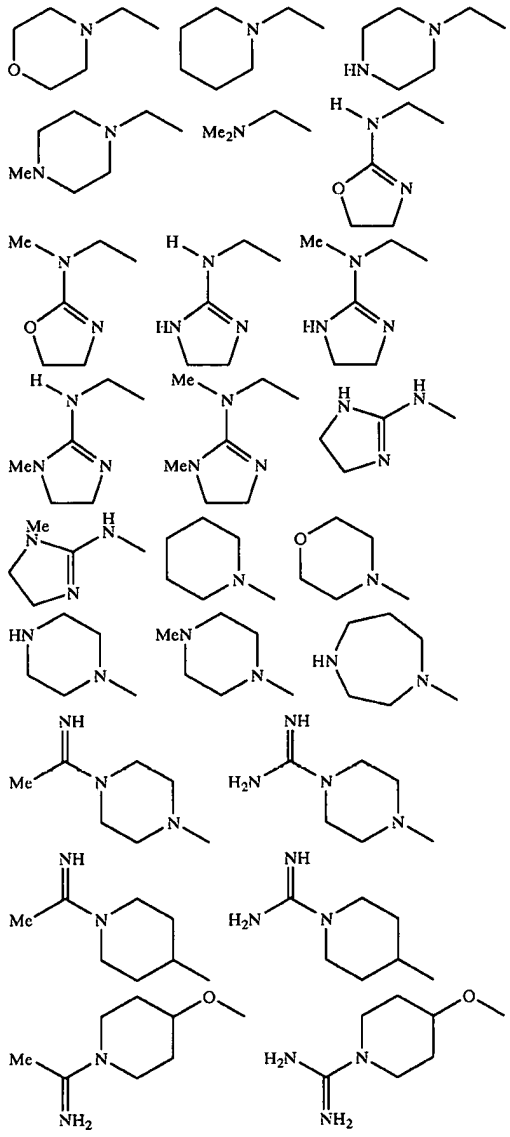
R^{1a} is a member selected from the group consisting of:

H, —F, —Cl and —Br;

R^{1e} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; and

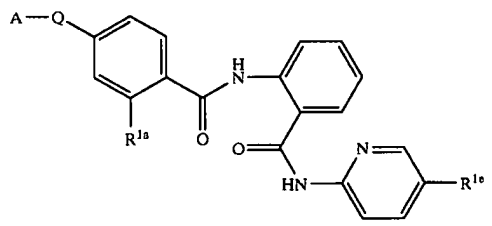
A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another further preferred embodiment of the invention are compounds according to the formula (IV):

(IV)



where:

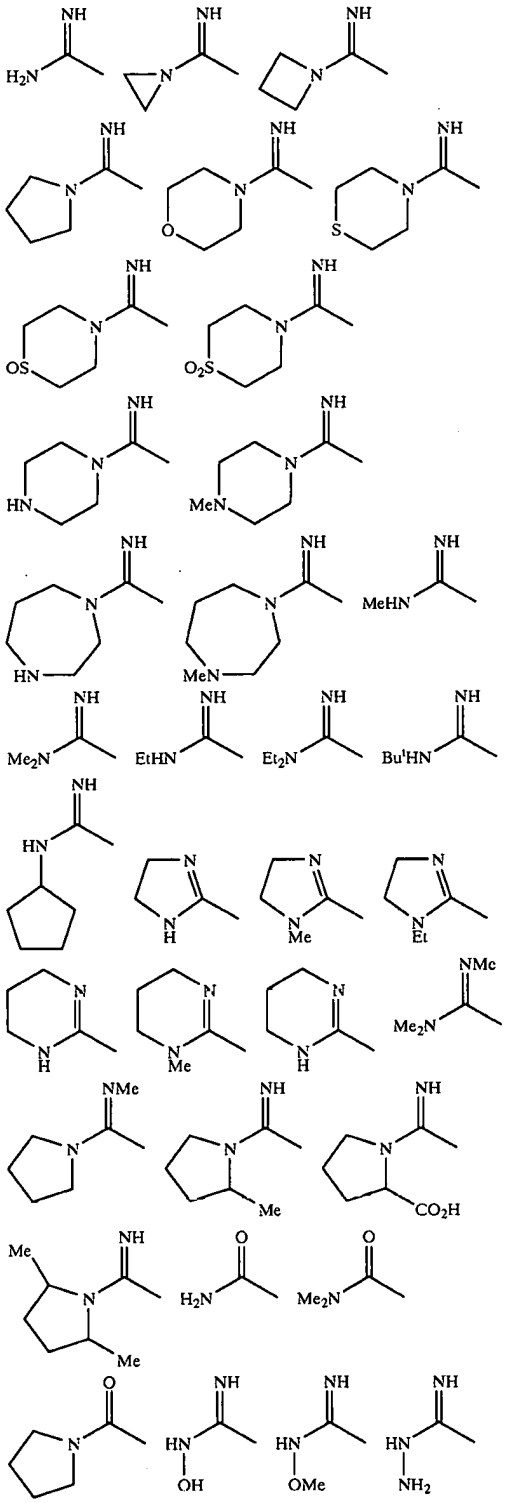
R^{1a} is a member selected from the group consisting of:

H, —F, —Cl and —Br;

R^{1e} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2;

A-Q is a member selected from the group consisting of:



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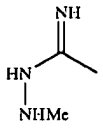
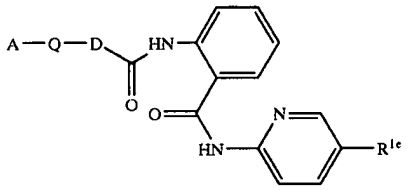


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Still another preferred embodiment of the invention are compounds of formula (V):



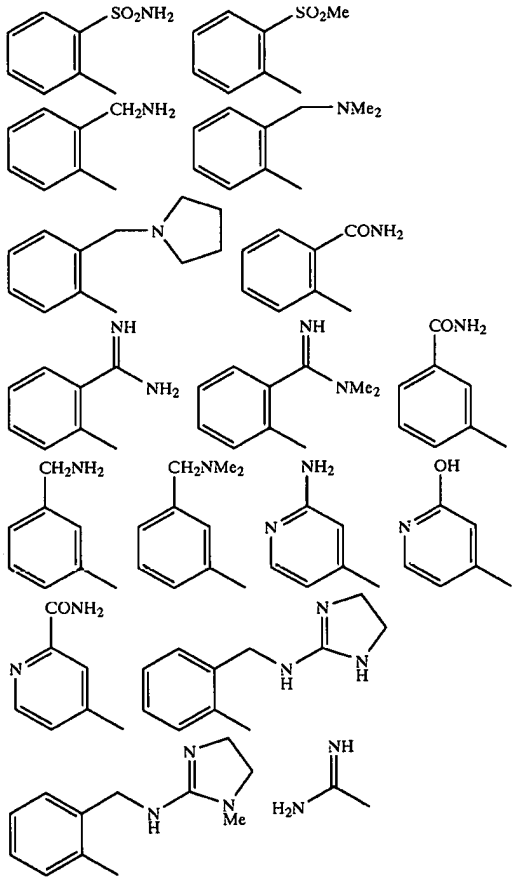
(V)

where:

R^{1e} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2;

A-Q is a member selected from the group consisting of:



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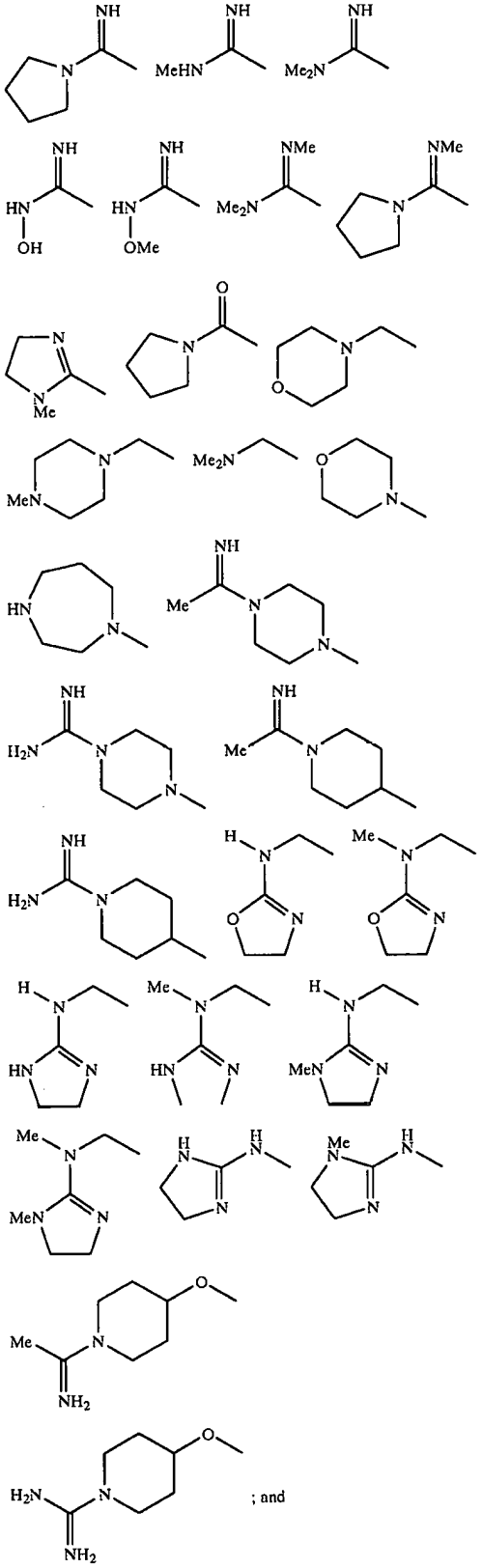
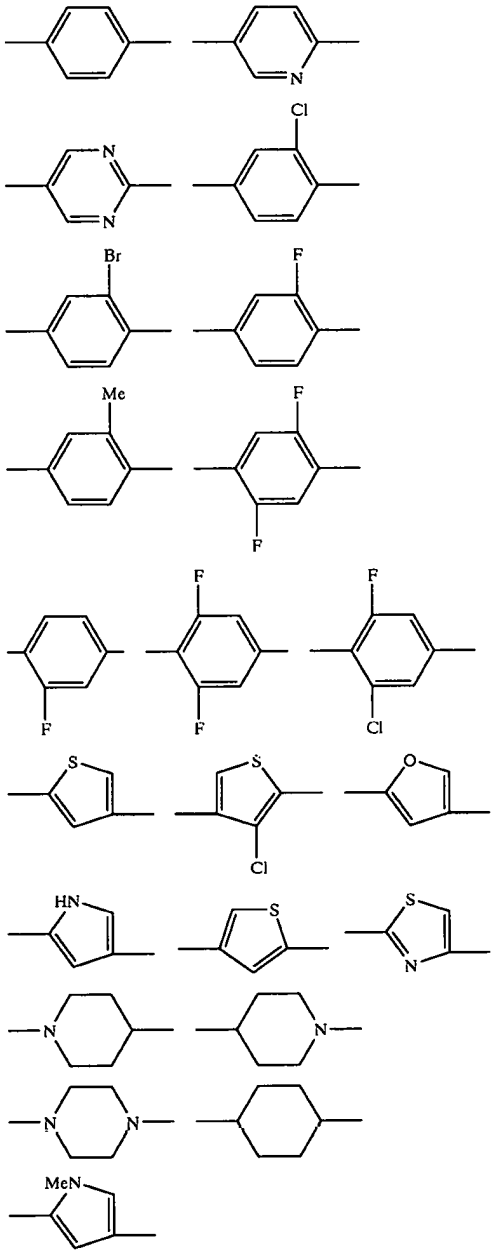


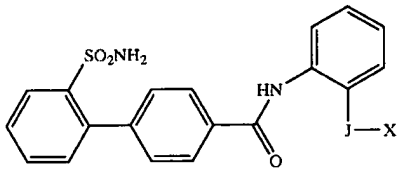
; and

D is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment, the present invention provides a compound according to the formula:



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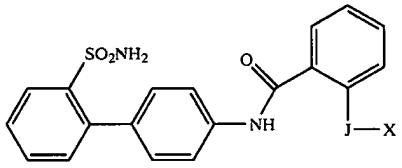
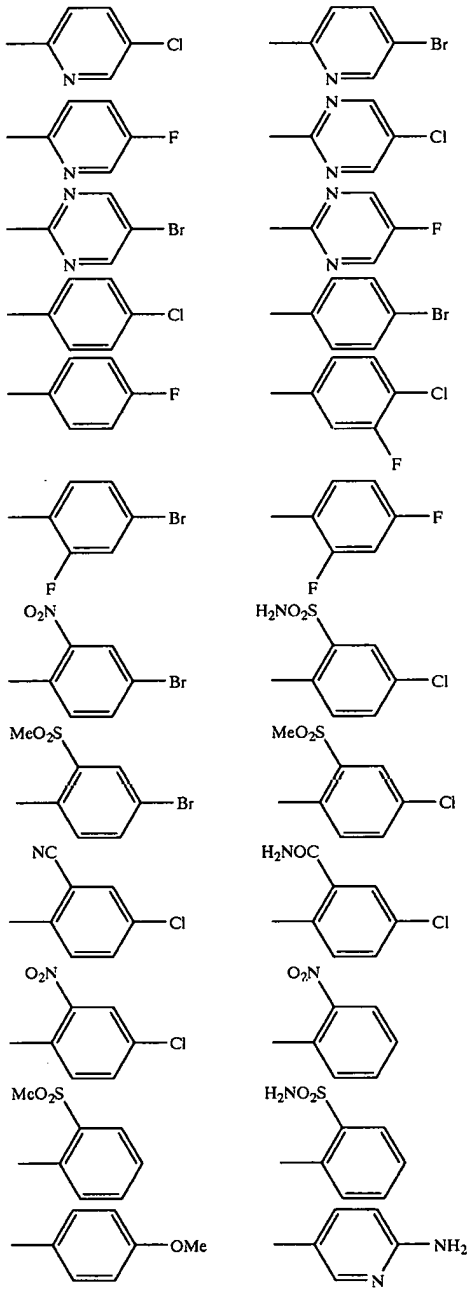


where:

J is a member selected from the group consisting of:

—NHC(═O)—, —C(═O)NH—;

X is a member selected from the group consisting of:



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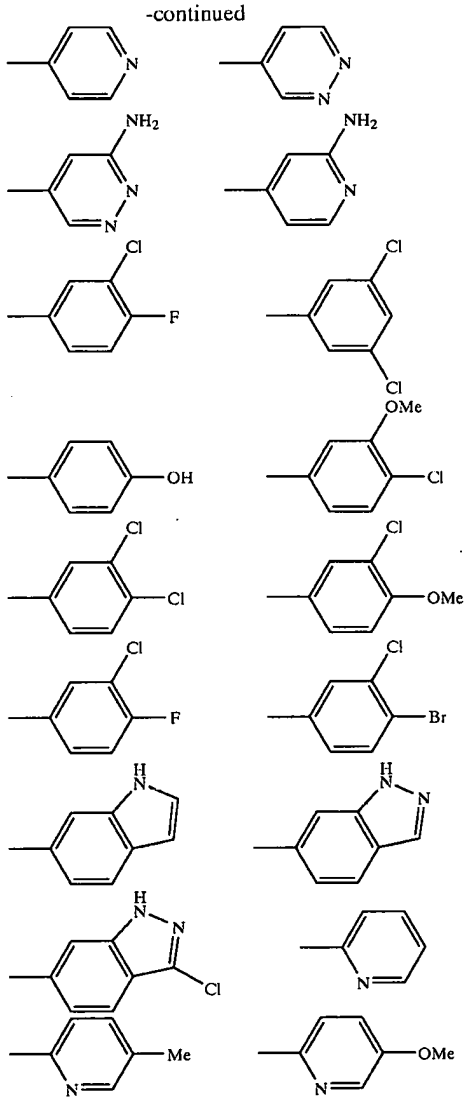
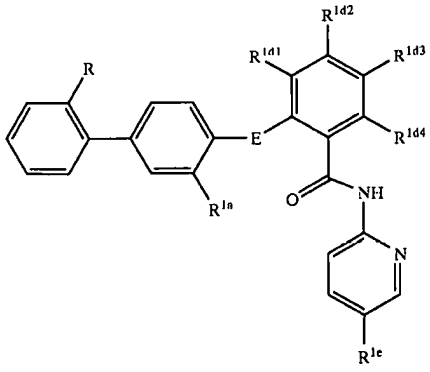


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment the present invention provides a compound according to the formula:



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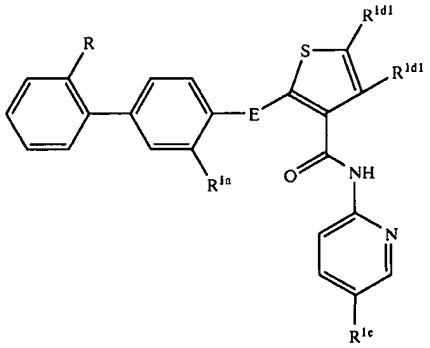
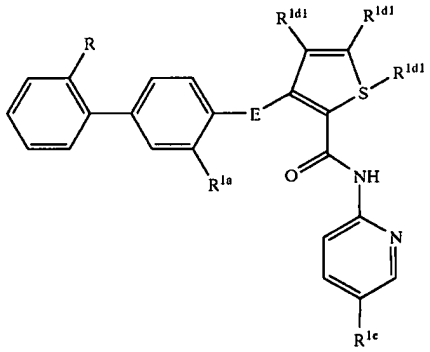




wherein:

R is a member selected from the group of:

—SO_2—NH_2 and —SO_2Me;

R^{1a} is a member selected from the group of:

H, —F, —Cl and Br;

E is a member selected from the group consisting of:

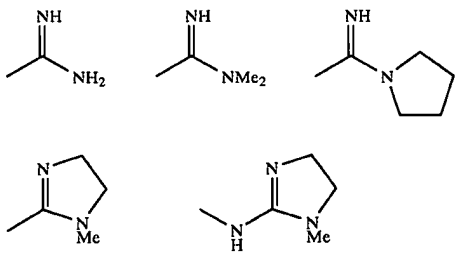
—NHC(=O)— and —C(=O)NH—;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, —F, —Cl, —Br, —Me, —NO_2, —OH, —OMe, —NH_2, —NHAc, —$NHSO_2Me$, —CH_2OH and —CH_2NH_2;

R^{1d3} is a member selected from the group of:

H, —CH_3, —CF_3, —Cl, —F, —Br, —NH_2, —$N(—Me)_2$, —OH, —OMe, —$NHSO_2Me$, —NO_2, —CN, —C(=O)—OMe, —CO_2H, —C(=O)—NH_2, —SO_2NH_2, —SO_2CH_3, —NHC(=O)—Me, —C(=O)—$N(—Me)_2$, —CH_2NH_2, —CH_2—$N(—Me)_2$, —CH_2OH, —OCH_2CO_2H, —$OCH_2C(=O)$—OMe, —$OCH_2C(=O)$—NH_2, and —$OCH_2C(=O)$—$N(—Me)_2$.



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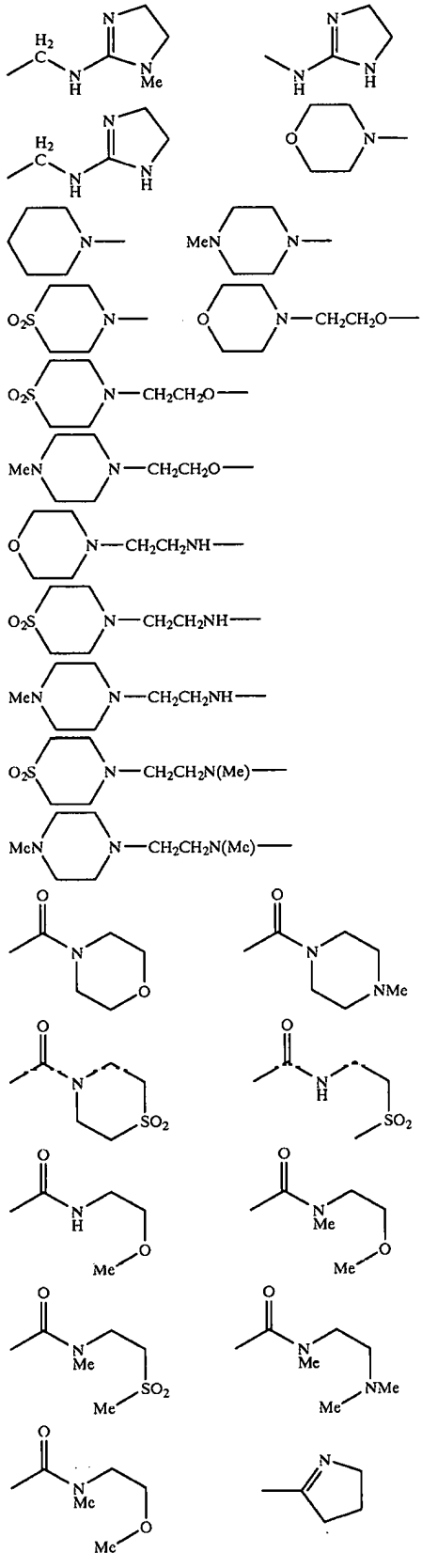

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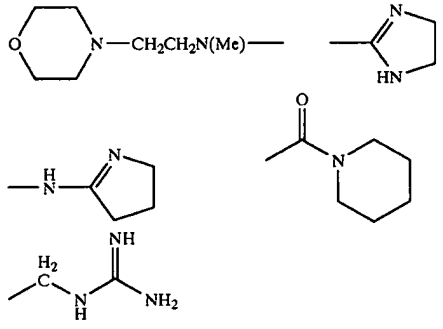
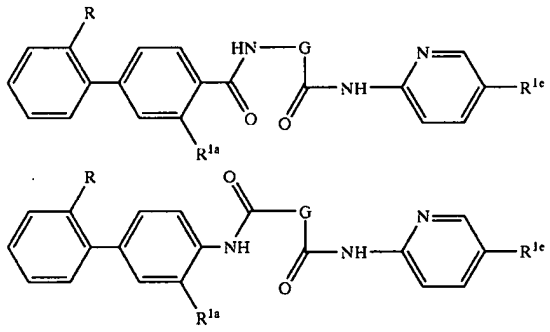


R^{1e} is a member selected from the group of:

F, —Cl, —Br, —OH, —Me and —OMe,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment, the present invention provides a compound according to the formula:



wherein:

R is a member selected from the group consisting of:

$—SO_2NH_2$, $—SO_2Me$;

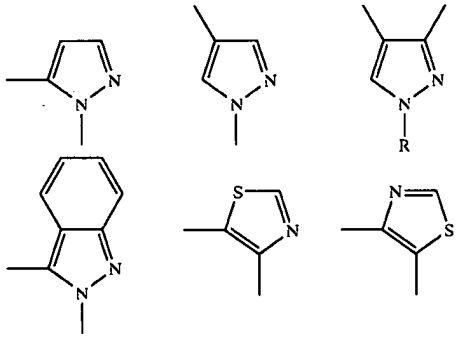
R^{1a} is a member selected from the group consisting of:

H, —F, —Cl and Br;

R^{1e} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OH, —Me, $—CF_3$ and $—CH_2NH_2$; and

G is a member selected from the group consisting of:



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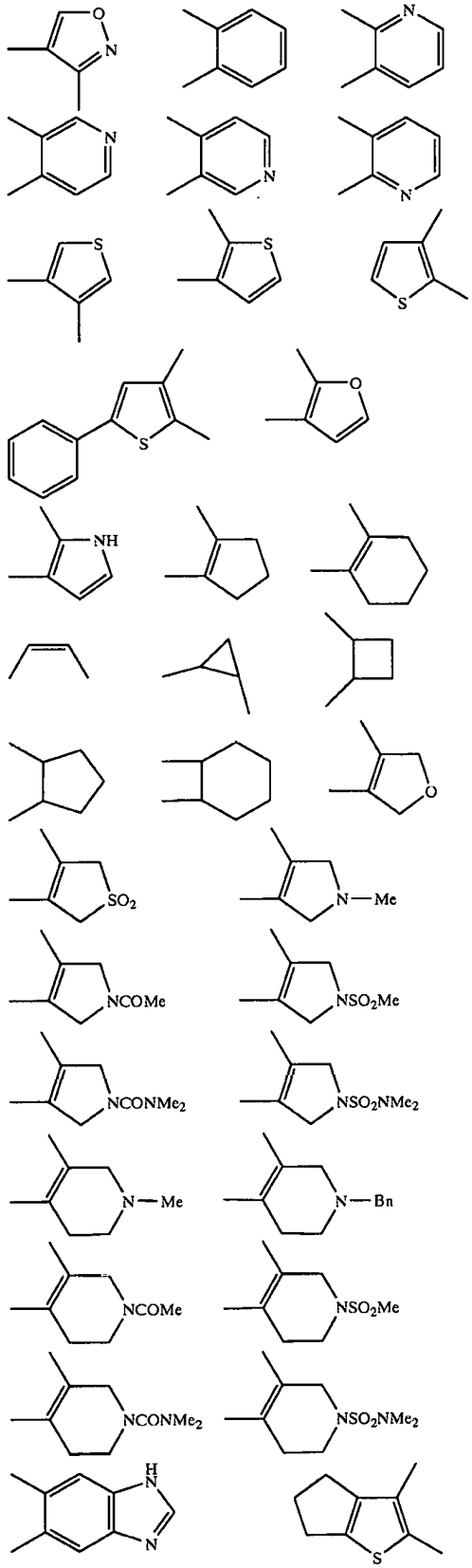

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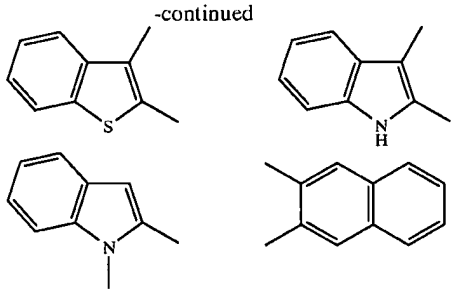
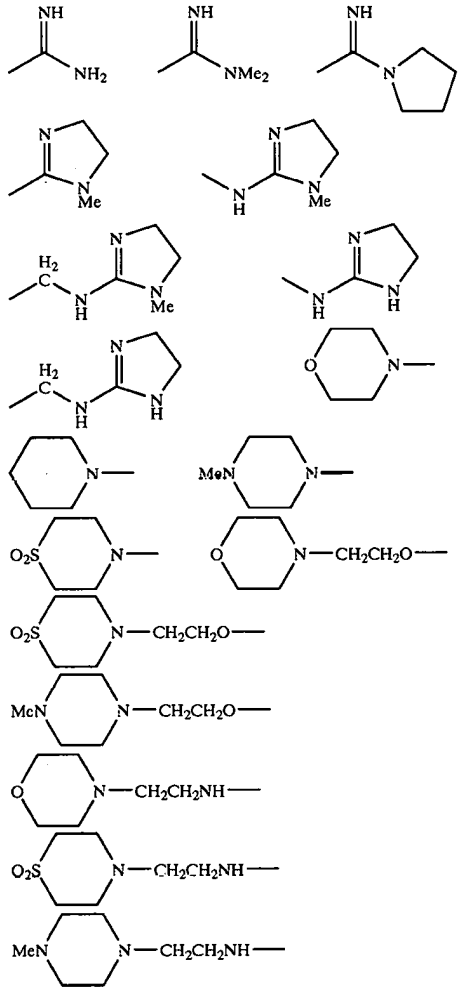


wherein each G group may be substituted by 0–4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

H, —CH_3, —CF_3, —Cl, —F, —Br, —NH_2, —N(—Me)$_2$, —OH, —OMe, —$NHSO_2Me$, —NO_2, —CN, —C(=O)—OMe, —CO_2H, —C(=O)—NH_2, —SO_2NH_2, —SO_2CH_3, —NH—C(=O)—Me, —C(=O)—N(—Me)$_2$, —CH_2NH_2, —CH_2—N(—Me)$_2$, —CH_2OH, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2C(=O)—NH_2, —OCH_2C(=O)—N(—Me)$_2$.



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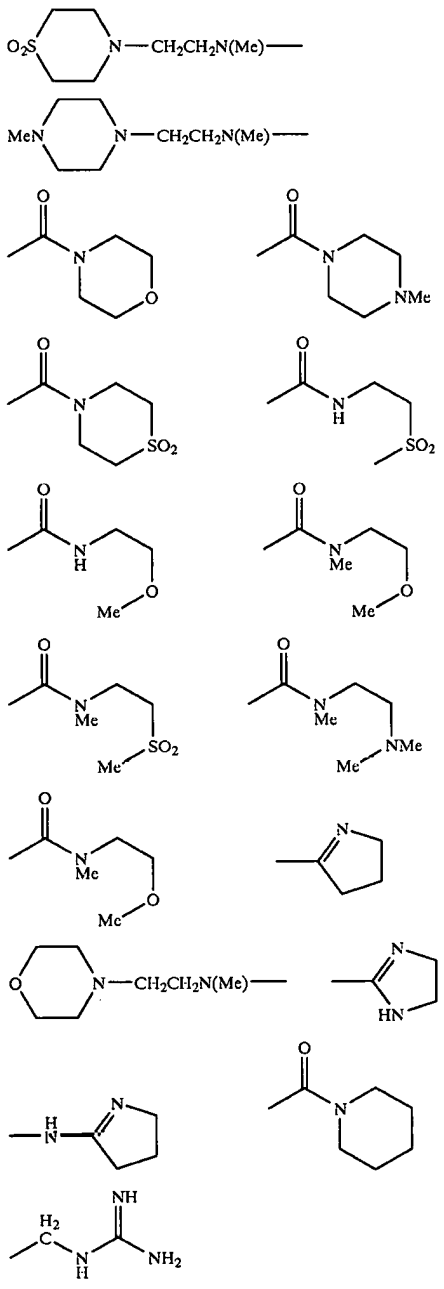
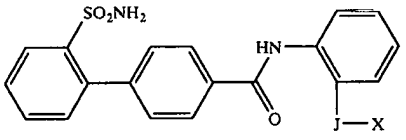


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



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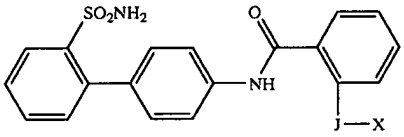
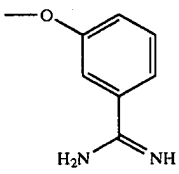
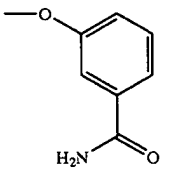
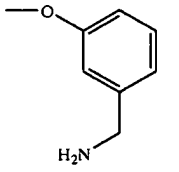
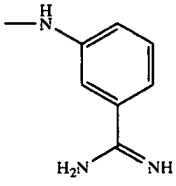
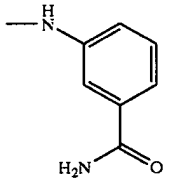
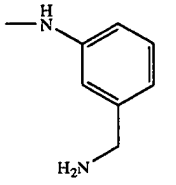
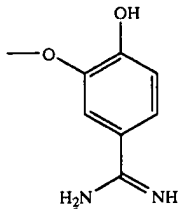
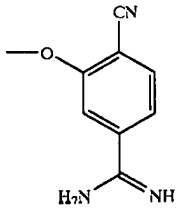
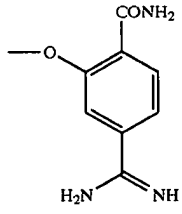
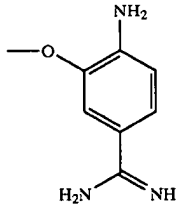
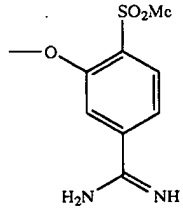
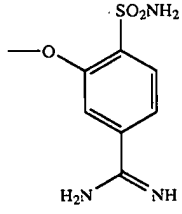


wherein:

J-X are collectively a member selected from the group consisting of:

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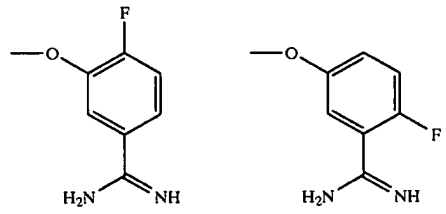
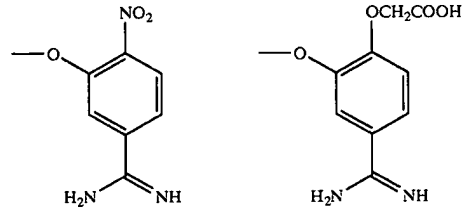
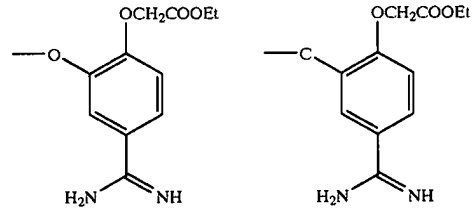
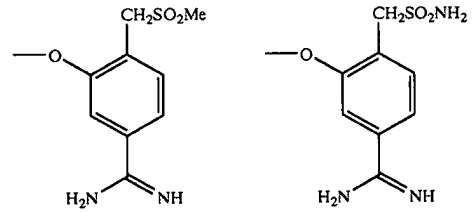
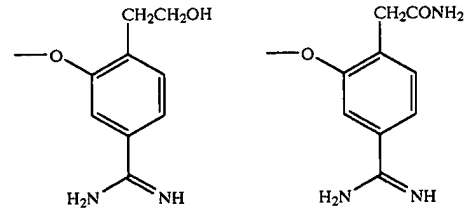
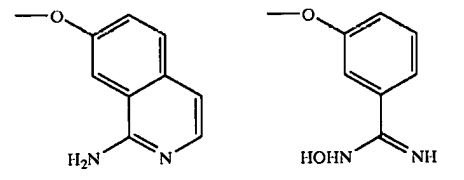
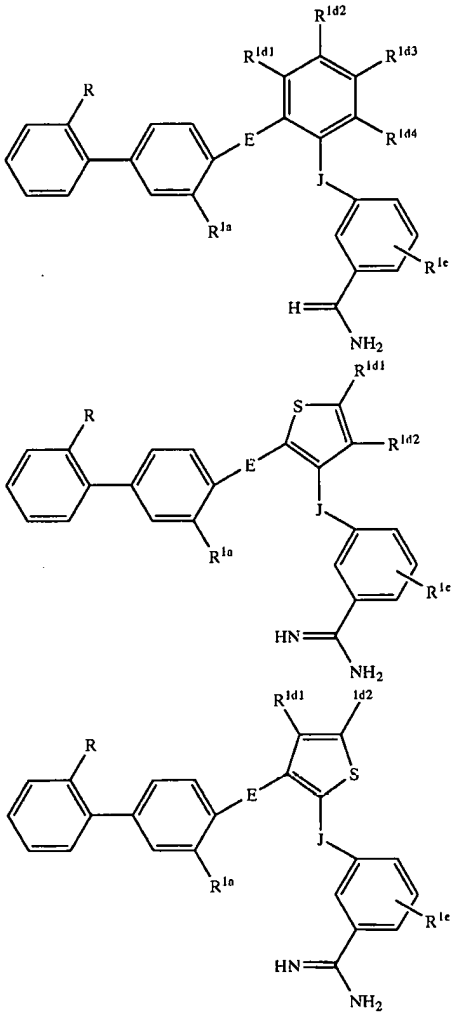
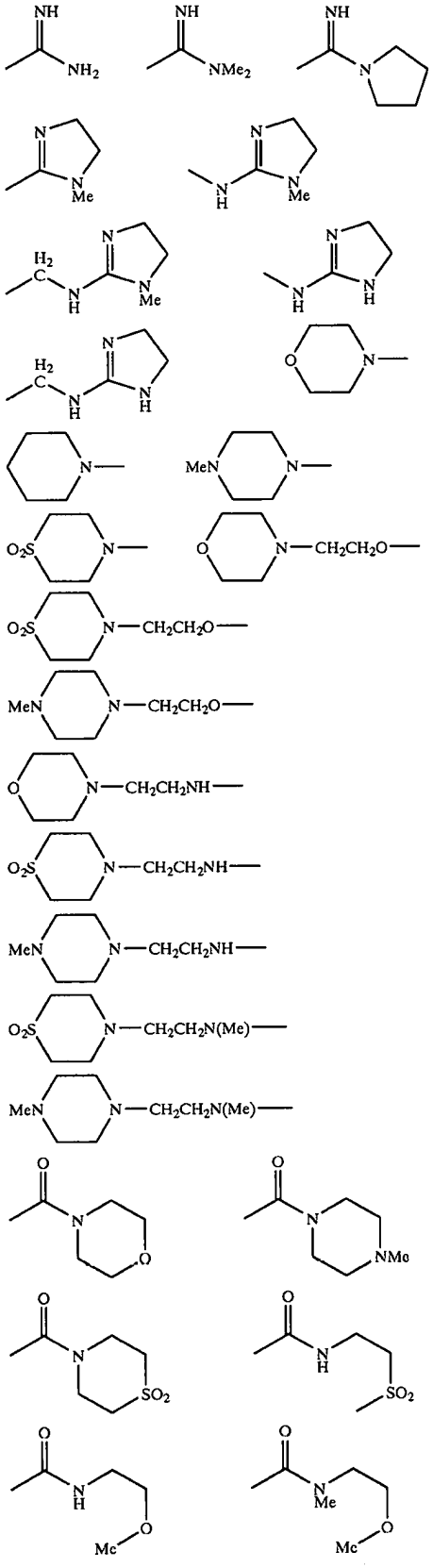







and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:





wherein:

R is a member selected from the group of:

—SO_2NH_2, and —SO_2Me;

R^{1d} is a member selected from the group of:

H, —F, —Cl and Br;

E is a member selected from the group consisting of:

—NHC(=O)— and —C(=O)NH—;

J is a member selected from the group consisting of:

—NHC(=O)— and —C(=O)NH—, O;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, —F, —Cl, —Br, —Me, —NO_2, —OH, —OMe, —NH_2, —NHAc, —$NHSO_2Me$, —CH_2OH, —CH_2NH_2;

R^{1d3} is a member selected from the group of:

H, —CH_3, —CF_3, —Cl, —F, —Br, —NH_2, —N(—Me)$_2$, —OH, —OMe, —$NHSO_2Me$, —NO_2, —CN, —CO_2Me, —CO_2H, —C(=O)—NH_2, —SO_2NH_2, —SO_2CH_3, —NHC(=O)—Me, —C(=O)—N(—Me)$_2$, —CH_2NH_2, —CH_2—N(—Me)$_2$, —CH_2OH, —OCH_2CO_2H, —OCH_2C(=O)—OMe, —OCH_2C(=O)—NH_2, —OCH_2C(=O)—N(—Me)$_2$,

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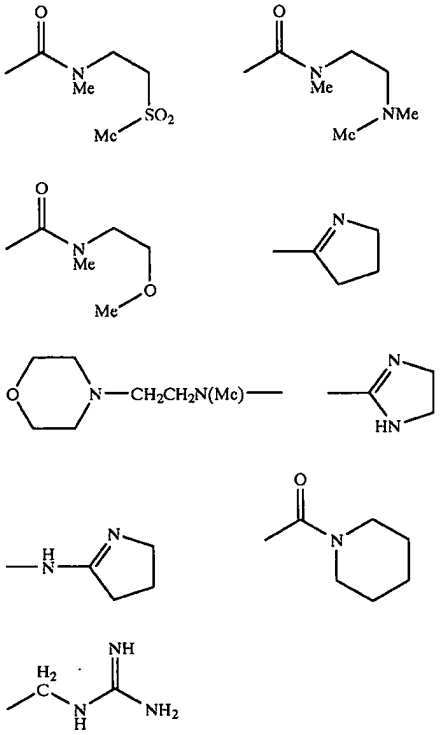

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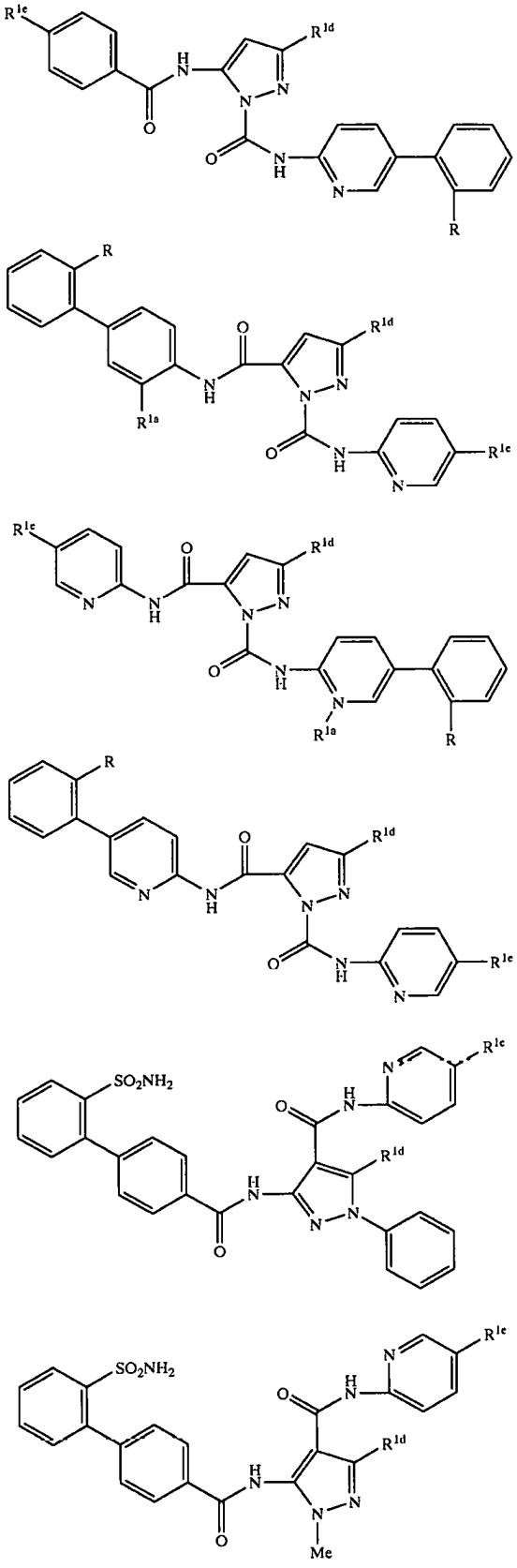
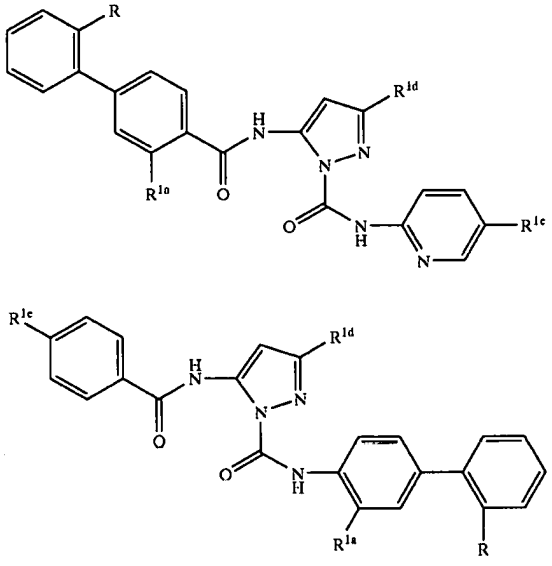


R^{1e} is a member selected from the group of:

F, —Cl, —Br, —OH, —Me and —OMe;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment, the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for G, particularly when G is a pyrazole ring structure.



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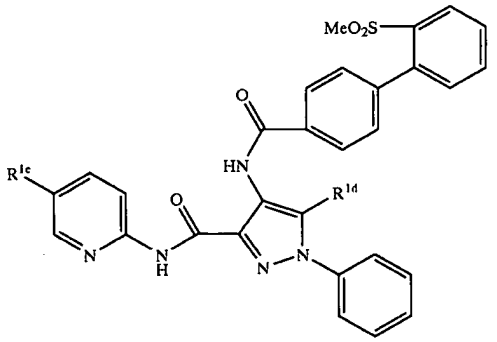
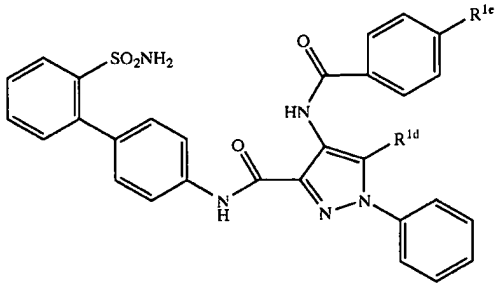
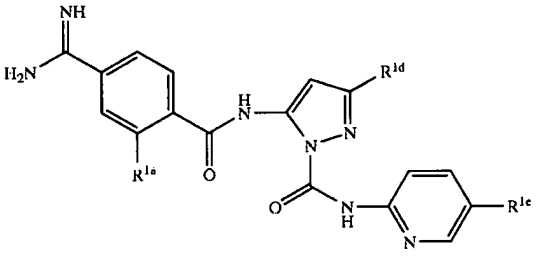
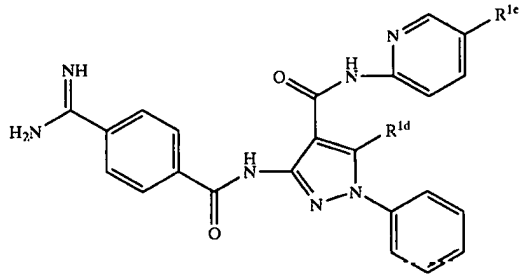








wherein:

R is a member selected from the group of:

—SO_2—NH_2, and —SO_2Me;

R^{1a} is a member selected from the group of:

H, —F, —Cl and Br;

R^{1d} is a member selected from the group of:

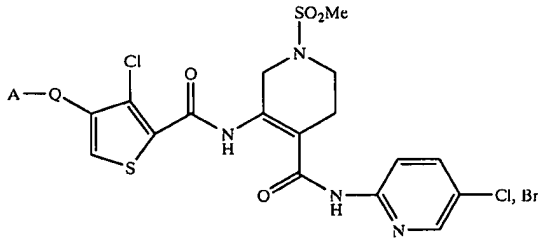
—H, —CH_3, —CF_3, —CN, —SO_2NH_2 and —SO_2CH_3; and

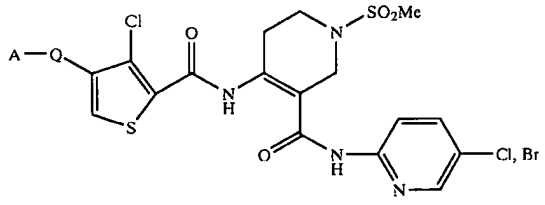
R^{1e} is a member selected from the group of:

—Cl and —Br;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

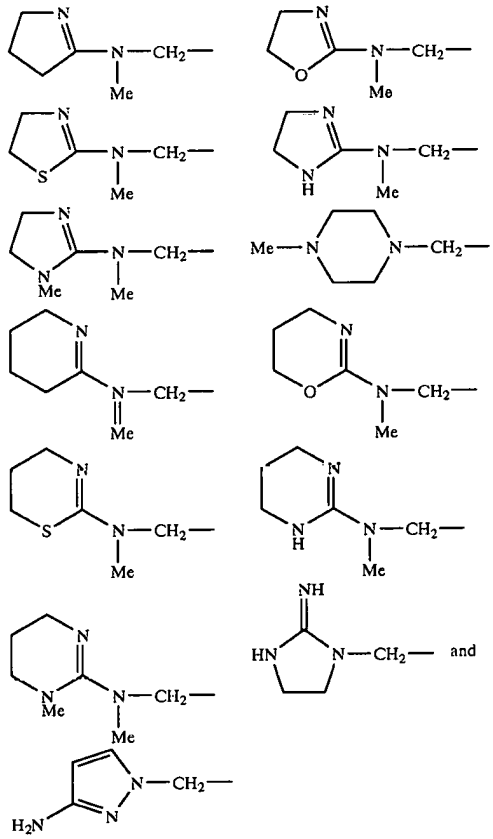
In another preferred embodiment, the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for A-Q taken collectively when the remainder of the compound structure has the one of the following two formulae:





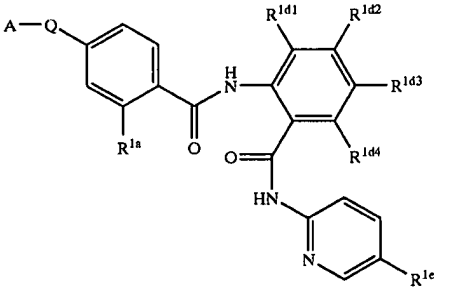
wherein:

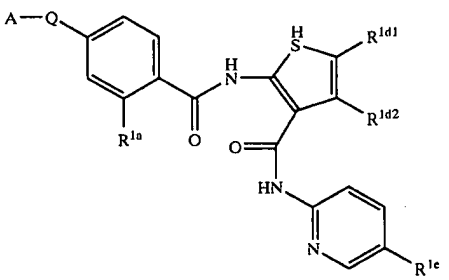
A-Q taken together are a member selected from the group consisting of:

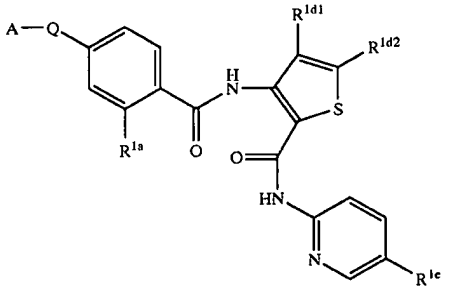


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment the present invention provides a compound according to the formula:

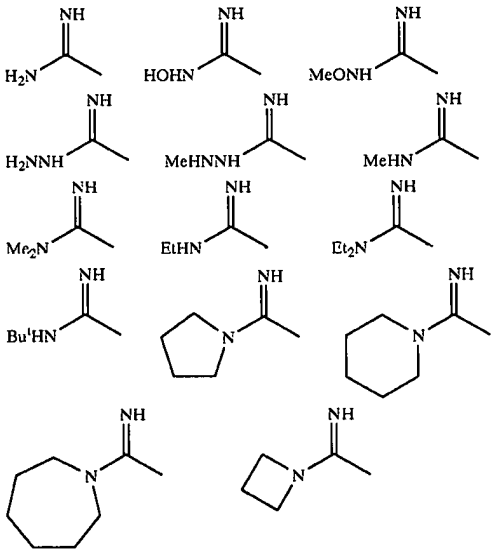






wherein:

A-Q is a member selected from the group of:



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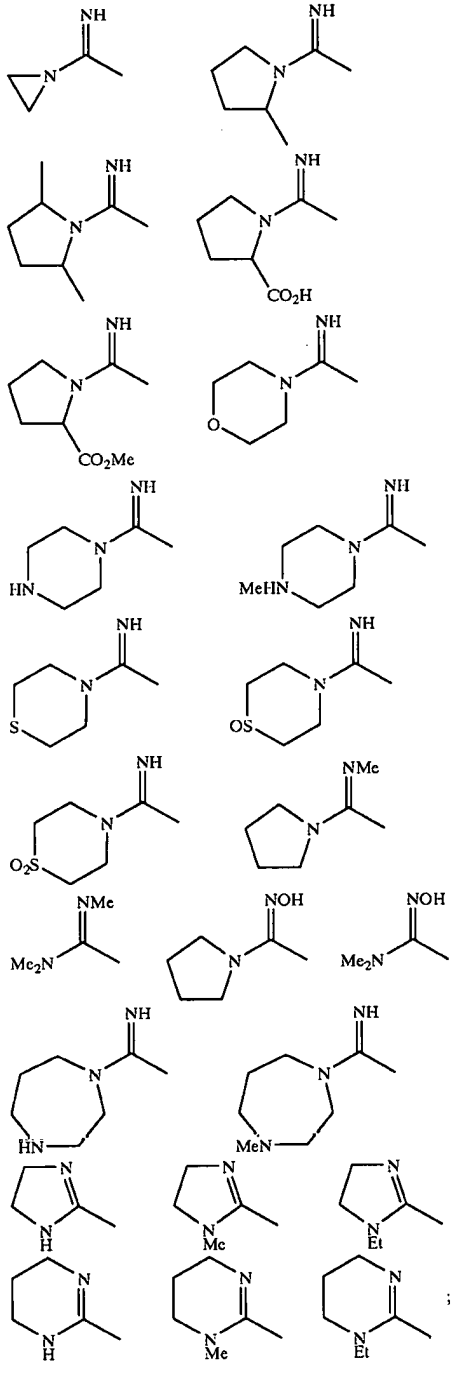


where A-Q may optionally be further substituted with at least one Z' group, where each Z' group is independently C_1–C_6 alkyl, preferably a C_1–C_3 alkyl group, most preferably a methyl group and where each Z' group may optionally be substituted with a hydroxyl, carboxylic acid or carboxylic acid C_1–C_6 ester group, preferably a hydroxyl, carboxylic acid or carboxylic acid C_1–C_3 ester group, and most preferably, a hydroxyl, carboxylic acid or carboxylic acid methyl ester;

R^{1a} is a member selected from the group of:

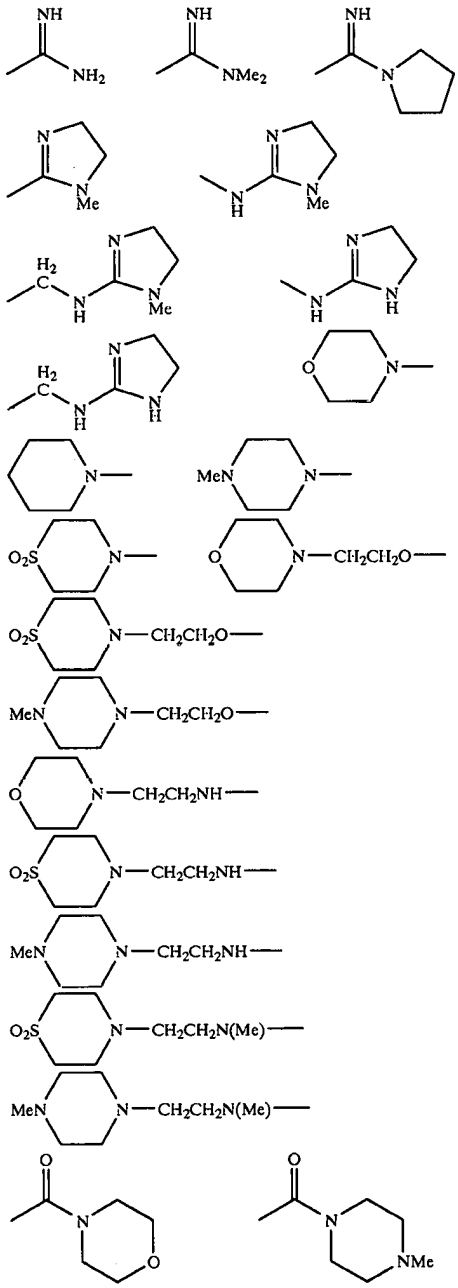
H, —F, —Cl and Br;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, —F, —Cl, —Br, —Me, $—NO_2$, —OH, —OMe, $—NH_2$, —NHAc, $—NHSO_2Me$, $—CH_2OH$, $—CH_2NH_2$

R^{1d3} is a member selected from the group of:

H, $—CH_3$, $—CF_3$, —Cl, —F, —Br, $—NH_2$, $—N(—Me)_2$, —OH, —OMe, $—NHSO_2Me$, $—NO_2$, —CN, $—C(=O)—OMe$, $—CO_2H$, $—C(=O)—NH_2$, $—SO_2NH_2$, $—SO_2CH_3$, $—NHC(=O)—Me$, $—C(=O)—N(Me)_2$, $—CH_2NH_2$, $—CH_2—N(—Me)_2$, $—CH_2OH$, $—OCH_2CO_2H$, $—OCH_2C(=O)—OMe$, $—OCH_2C(=O)—NH_2$, $—OCH_2C(=O)—N(—Me)_2$,



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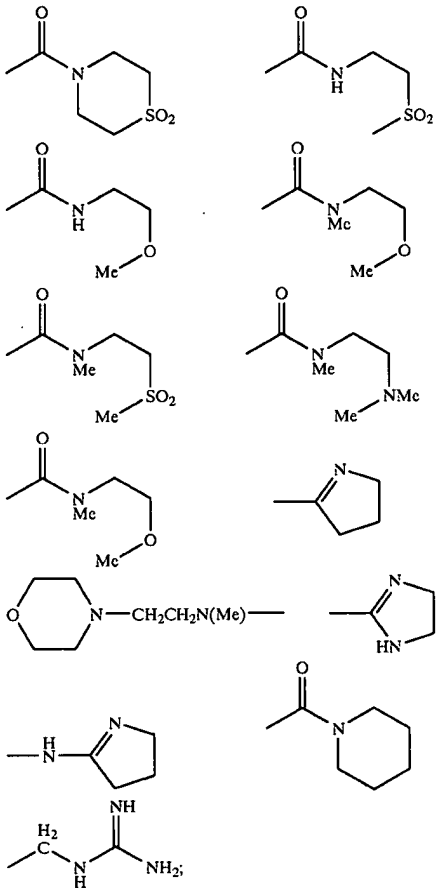


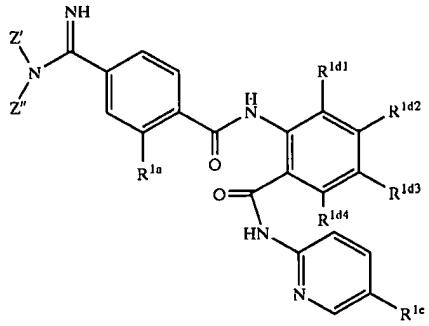
R^{1e} is a member selected from the group of:

F, —Cl, —Br, —OH, —Me and —OMe;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment, the invention provides a compound of formula VI:

(VI)



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In formula VI:

Z' and Z" are each independently a C_1–C_6 alkyl, preferably a C_1–C_3 alkyl group, most preferably a methyl group; where Z' and Z" may be optionally substituted with a

hydroxyl, carboxylic acid or carboxylic acid C_1–C_6 ester group, preferably a hydroxyl, carboxylic acid or carboxylic acid C_1–C_3 ester group, and most preferably, a hydroxyl, carboxylic acid or carboxylic acid methyl ester;

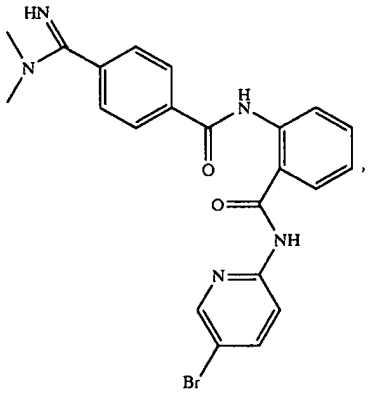
R^{1a} is a member selected from the group of H, —F, —Cl and Br;

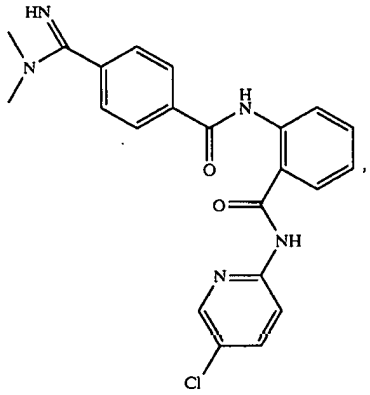
R^{1d1} and R^{1d4} are each H;

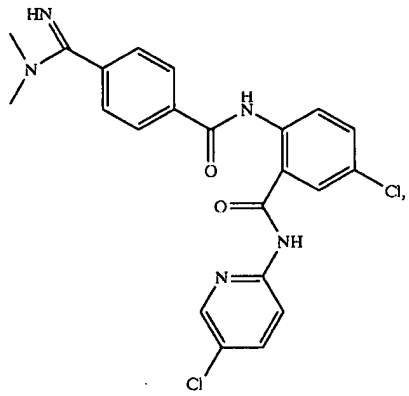
R^{1d1} and R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH and —OMe; and

R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe.

Examples of suitable compounds of formula VI, as described above, include, but are not limited to:







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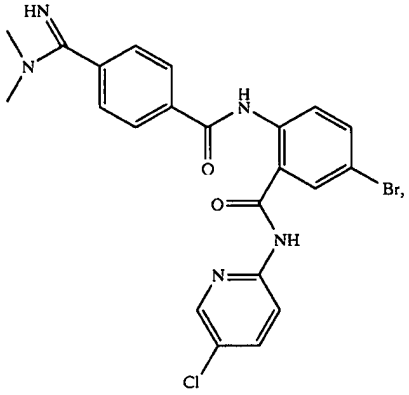

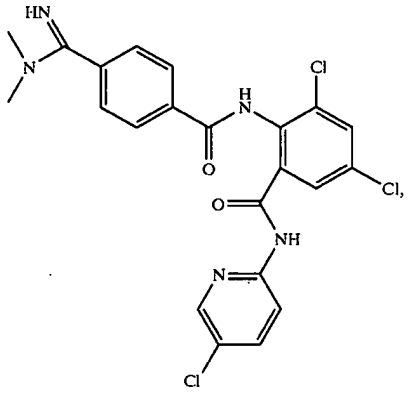

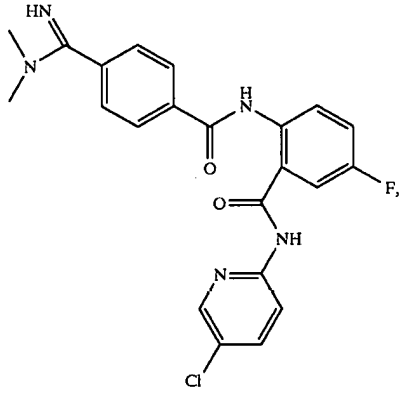

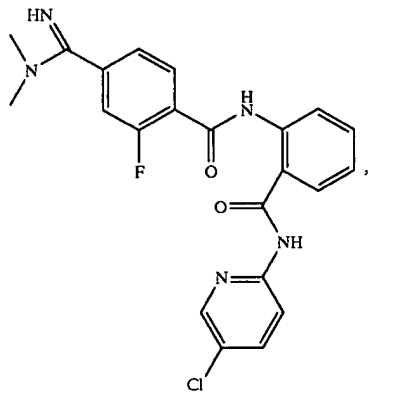

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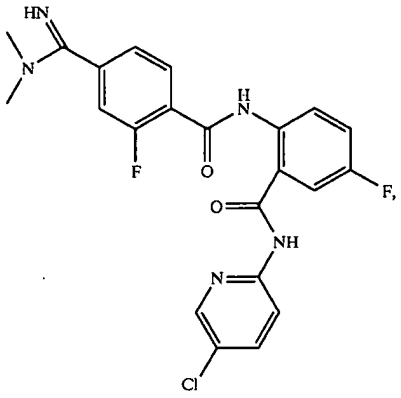

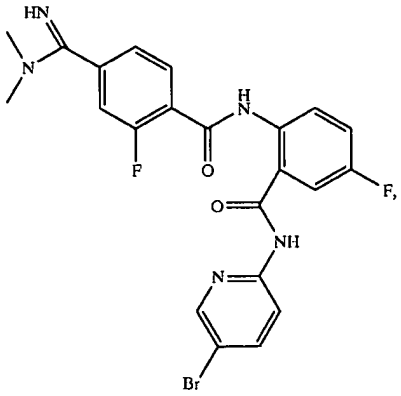

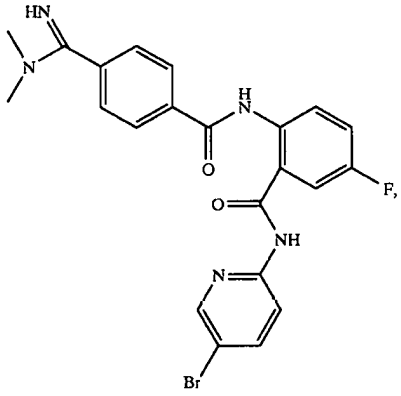

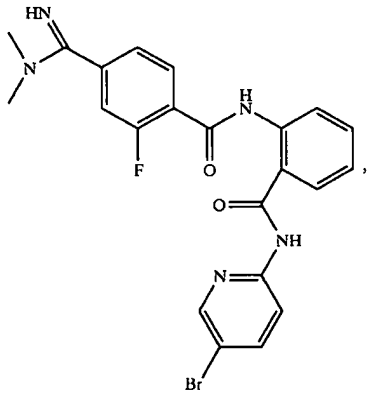

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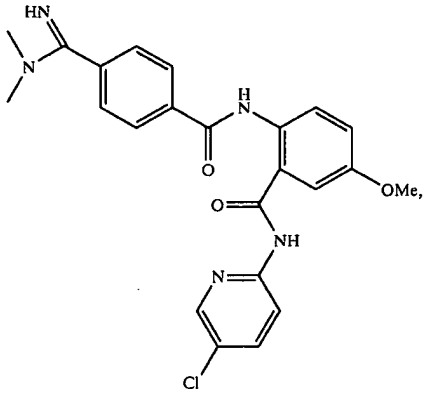

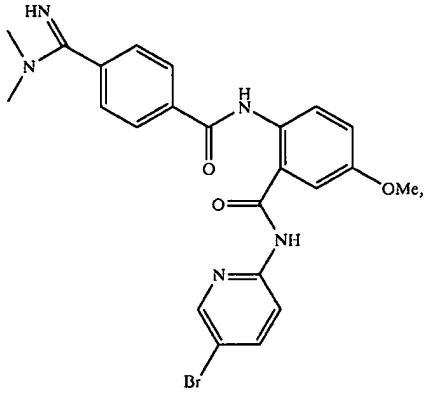

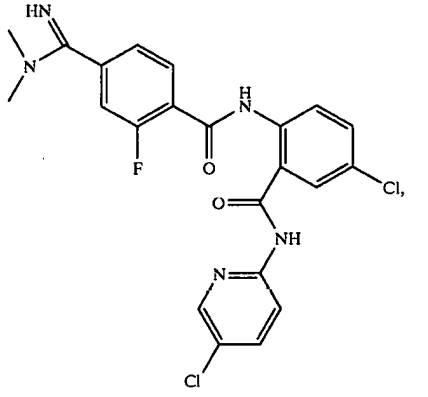

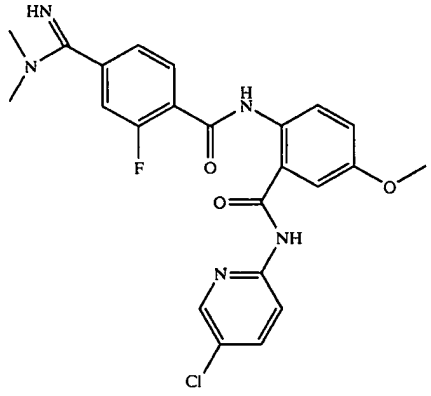

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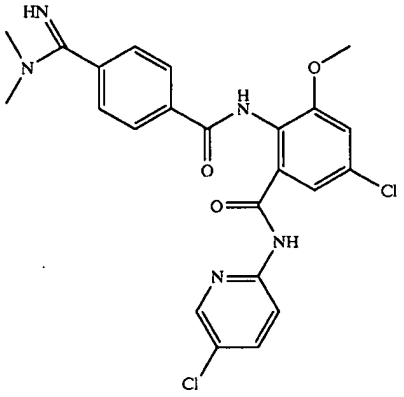
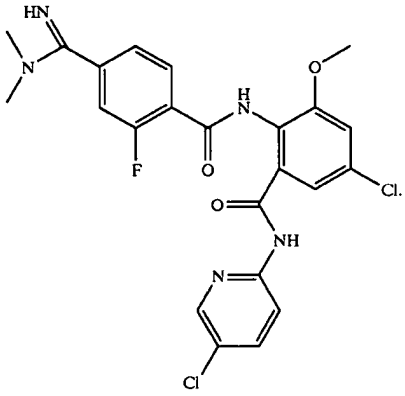
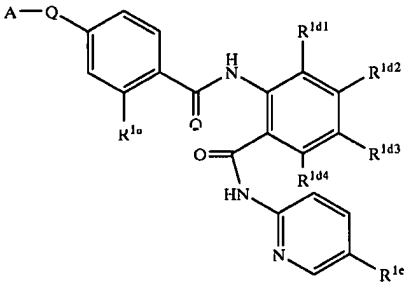


and



In another embodiment, the invention further provides a compound of formula VII:

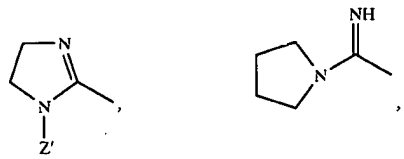


(VII)

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In formula VII:

A-Q is a member selected from the group of:



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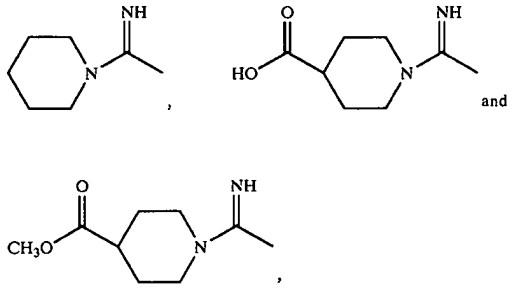


and

where Z' is as described above;

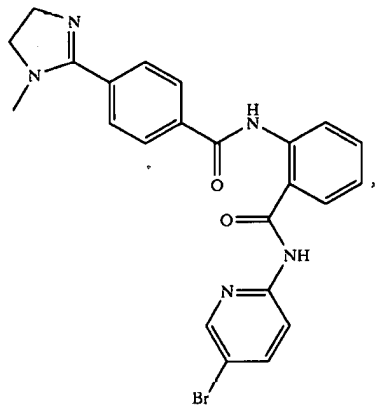
R^{1a} is a member selected from the group of H, —F, —Cl and Br;

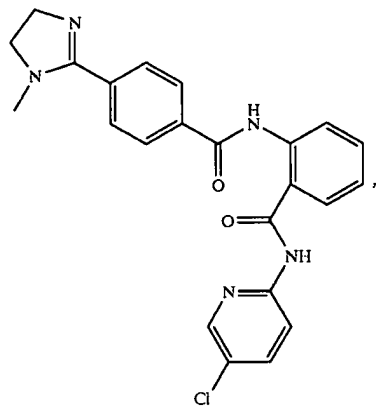
R^{1d2} and R^{1d4} are each H;

R^{1d1} is R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH and —OMe;

R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe.

Examples of suitable compounds of formula VII, as described above, include, but are not limited to:





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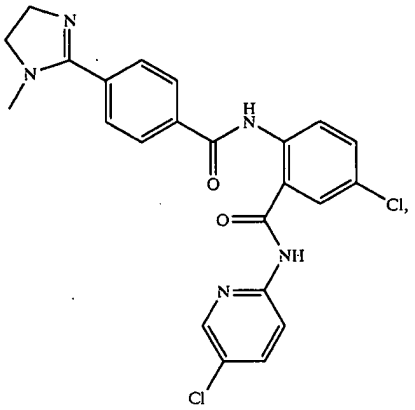

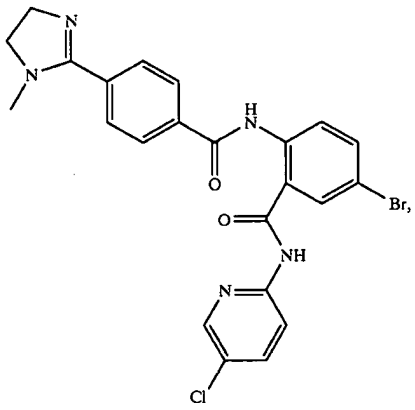

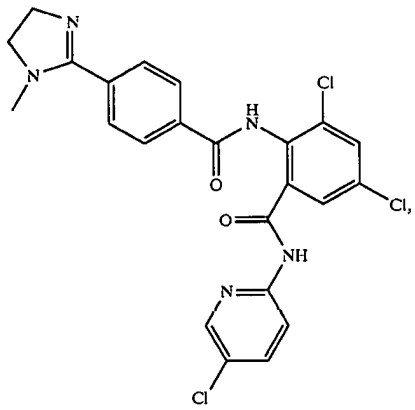

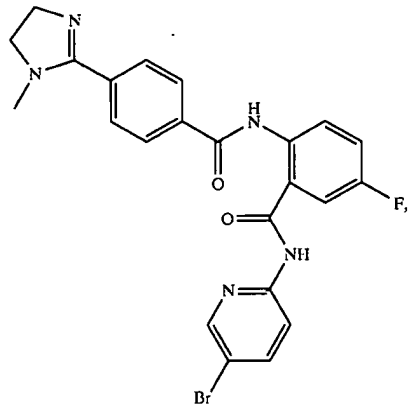

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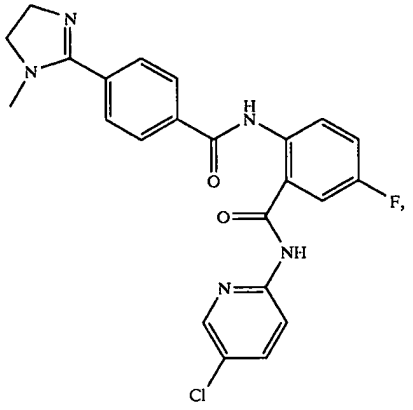

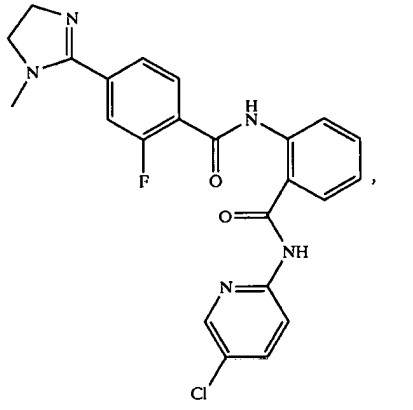

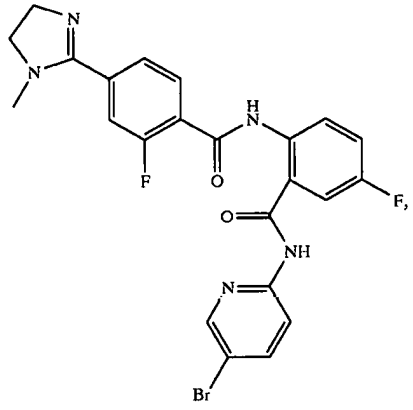

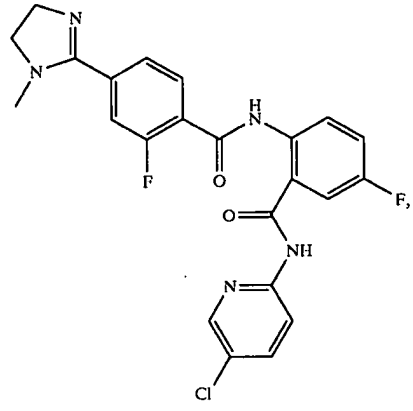

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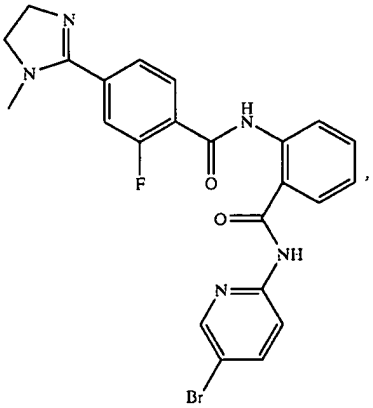

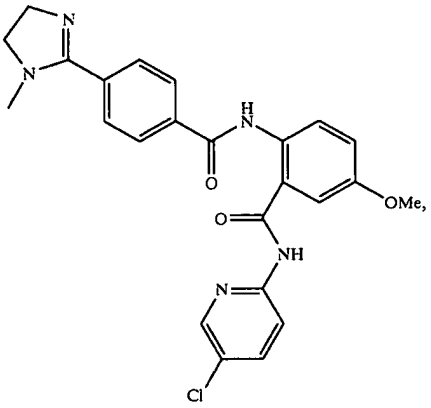

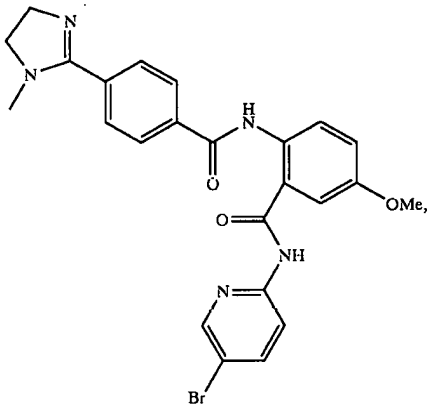

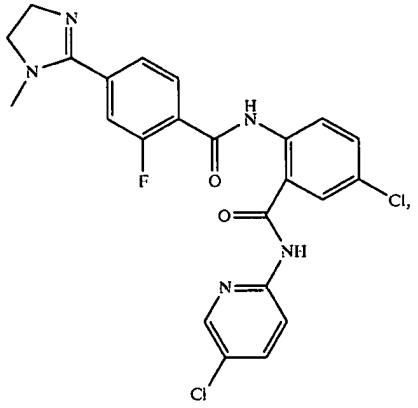

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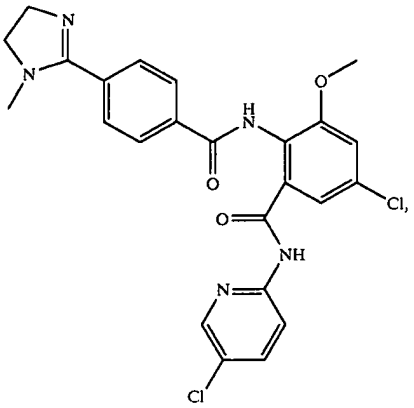

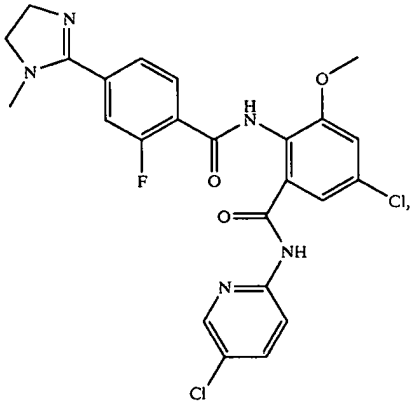

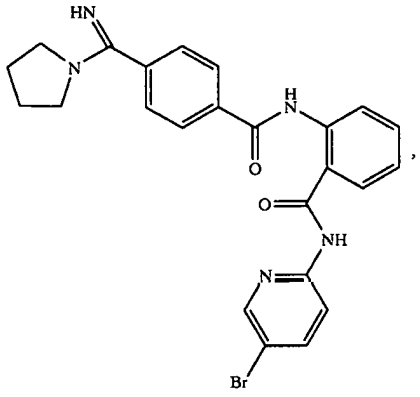

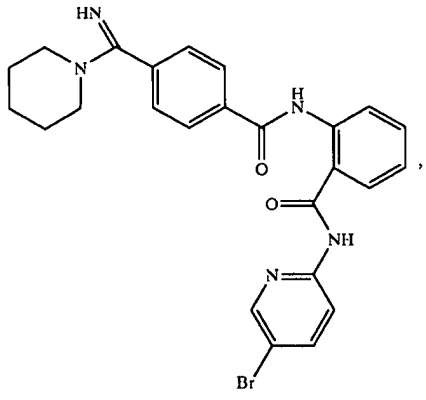

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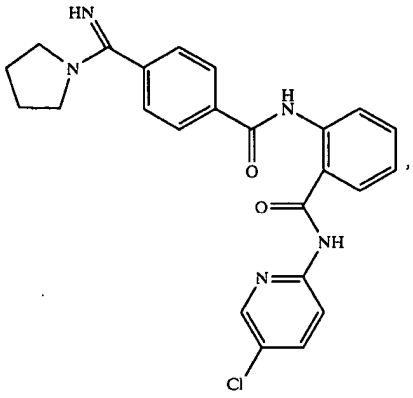

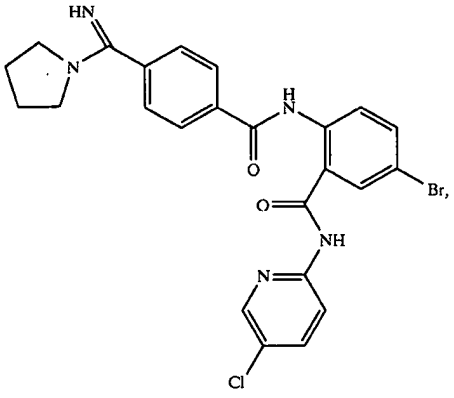

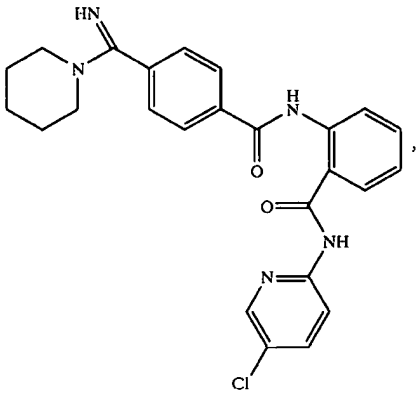

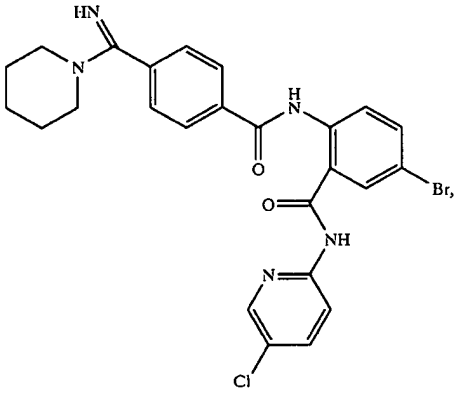

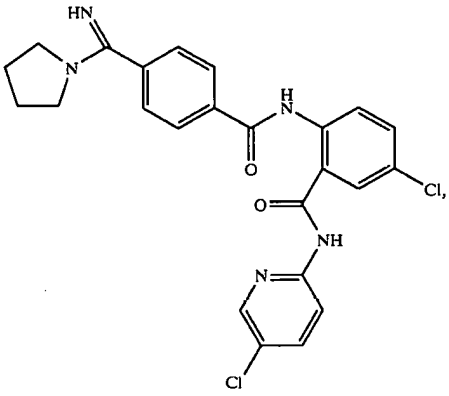

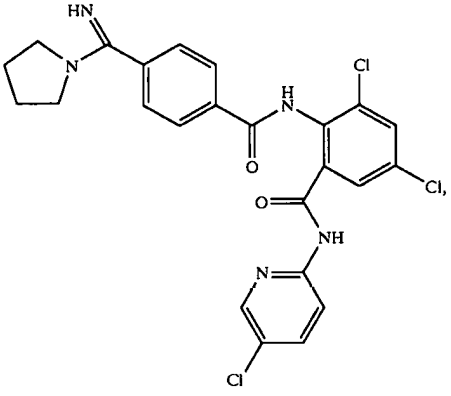

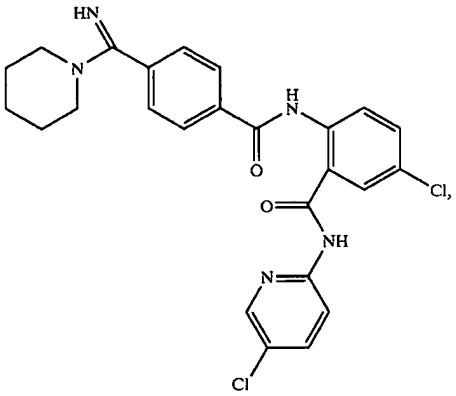

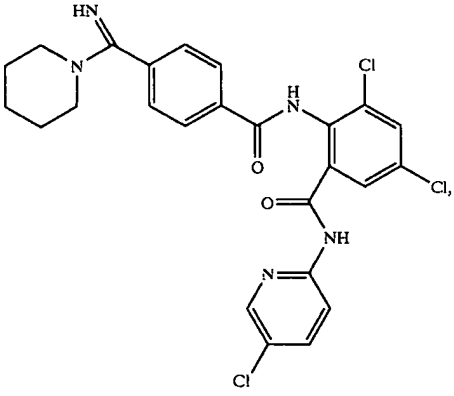

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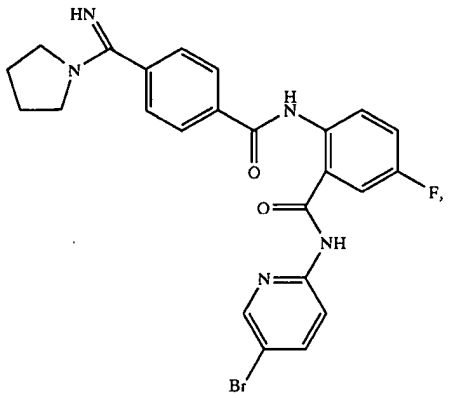

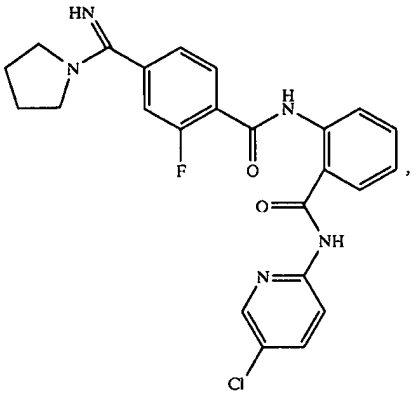

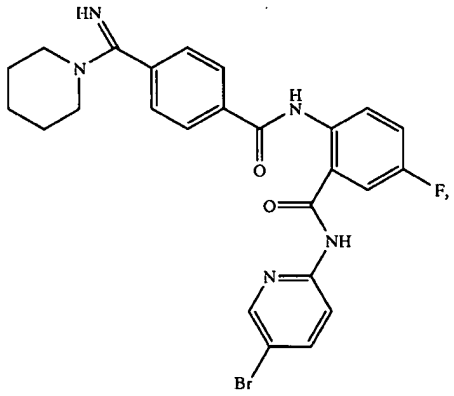

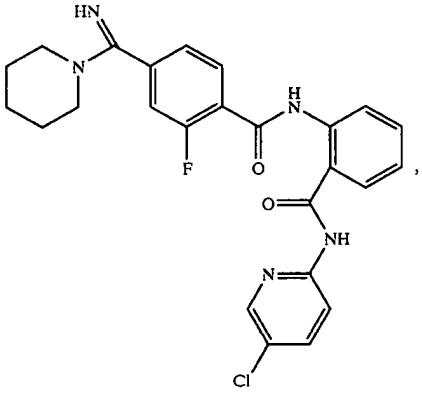

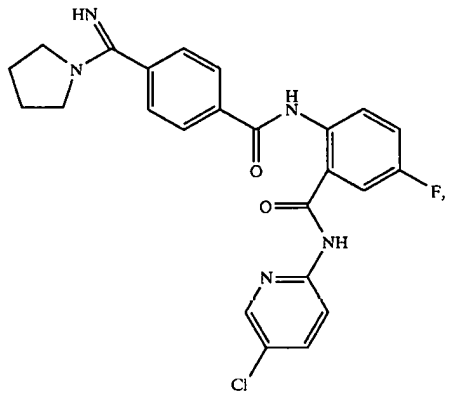

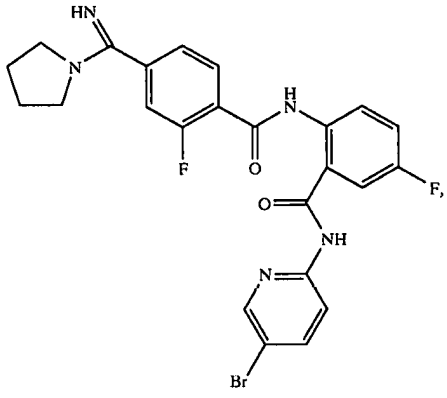

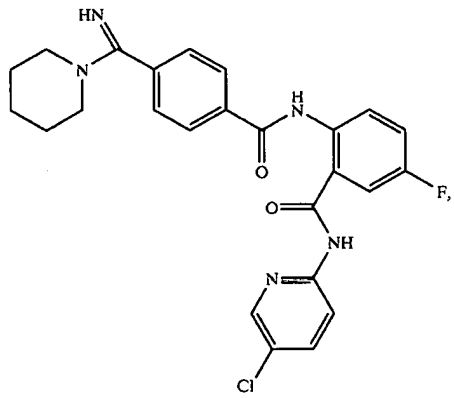

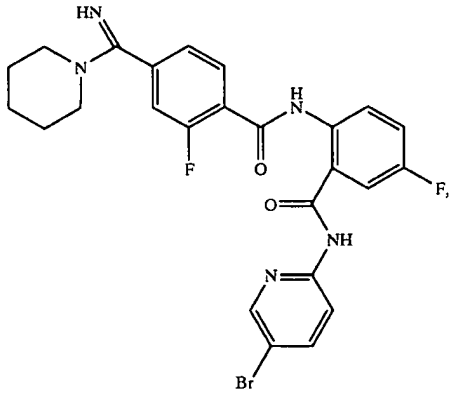

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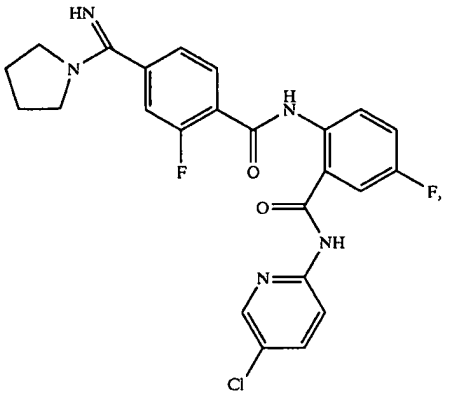

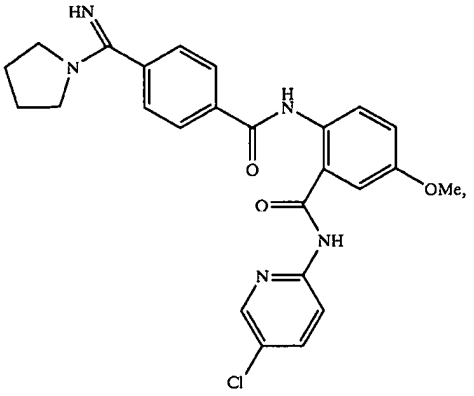

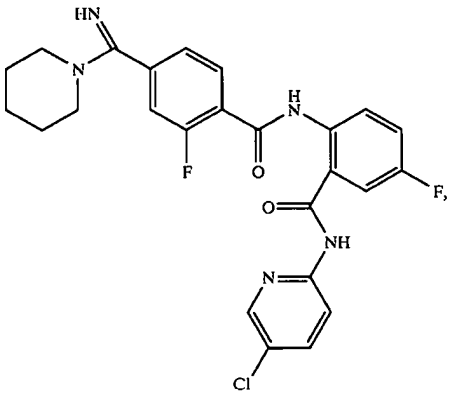

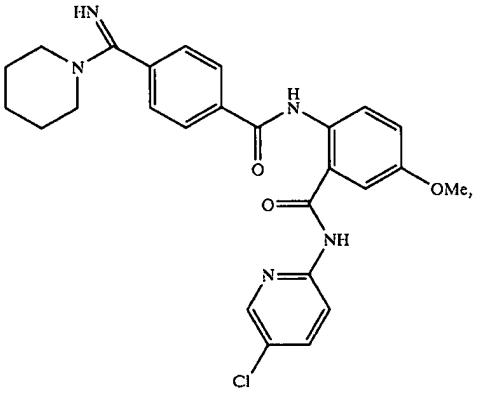

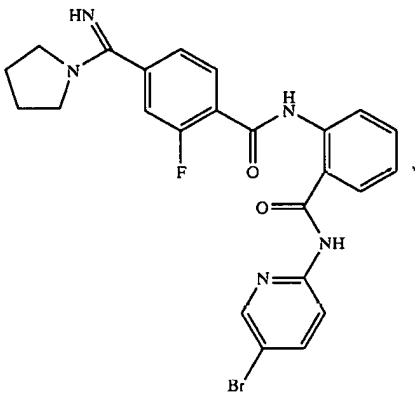

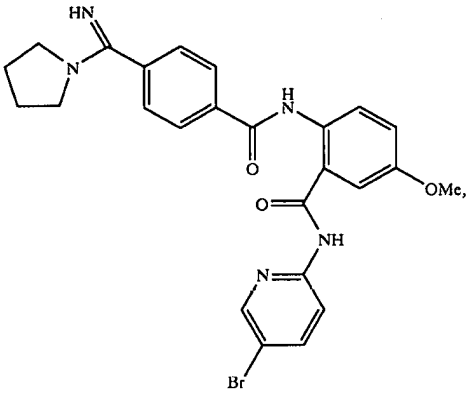

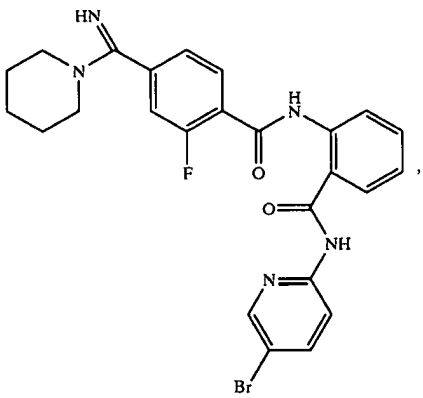

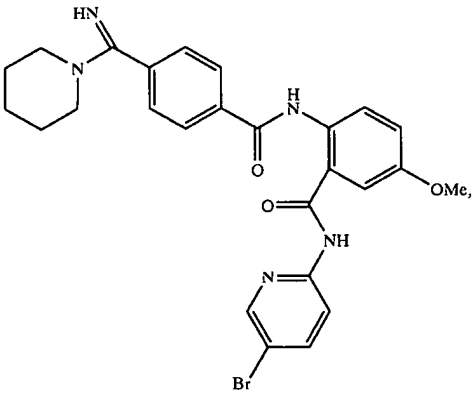

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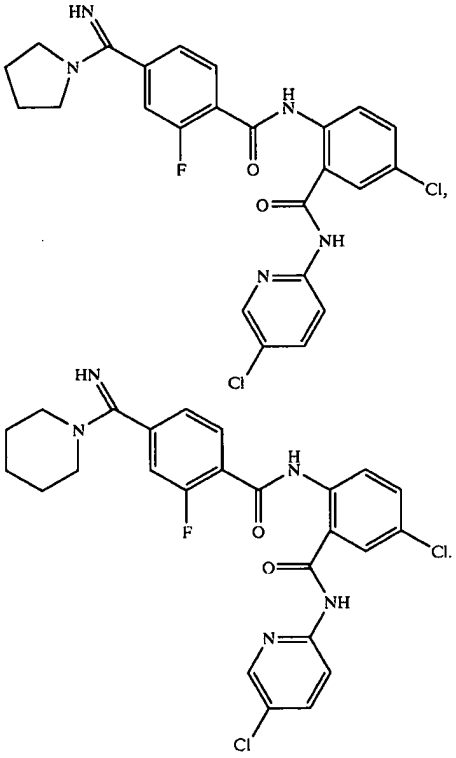

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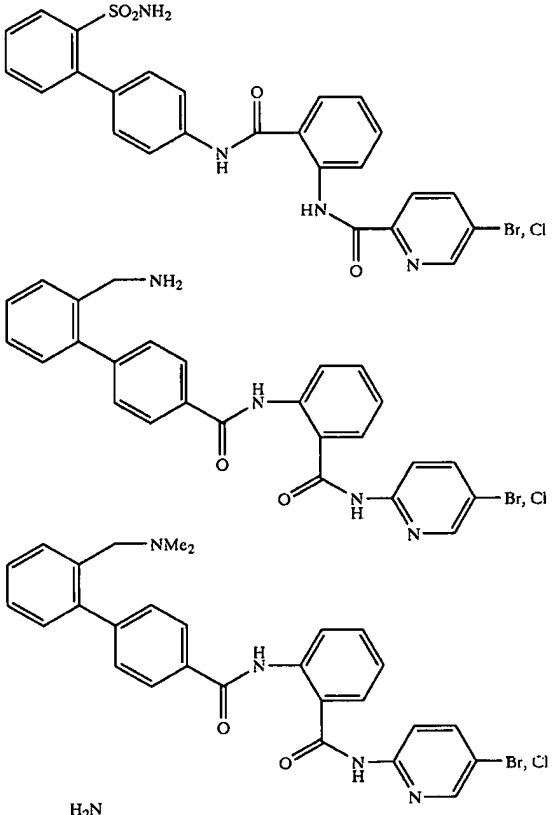
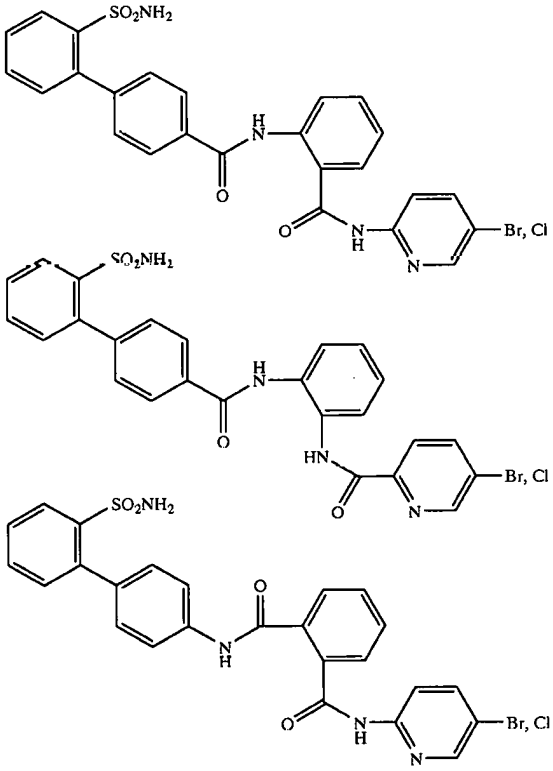
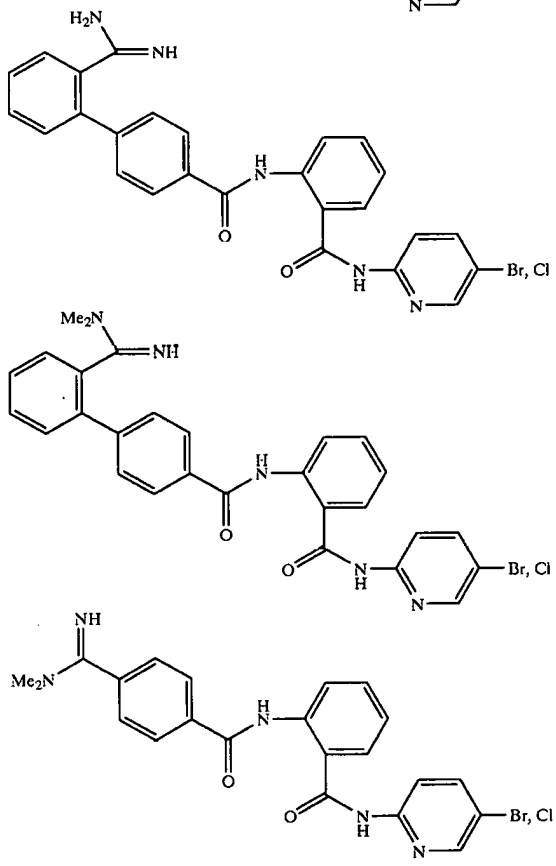


In another further preferred embodiment the present invention provides the following compounds:





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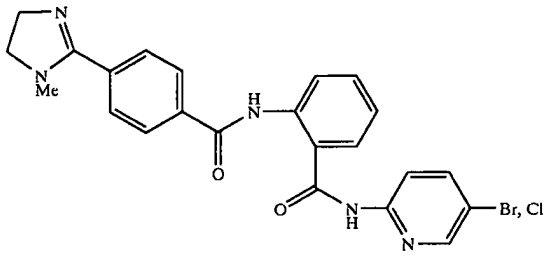

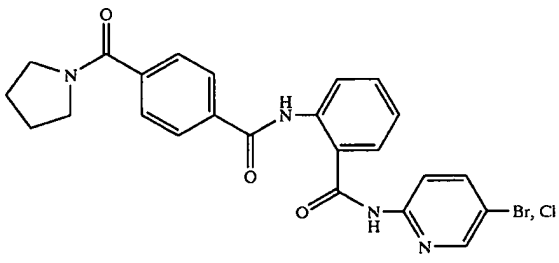

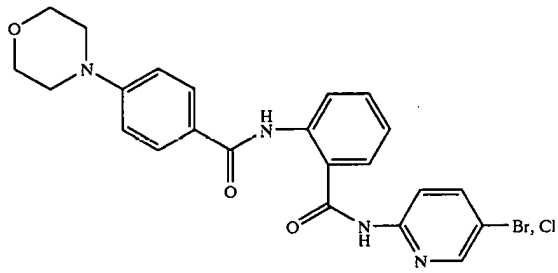

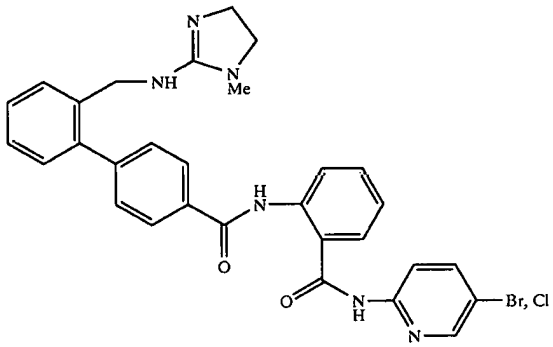

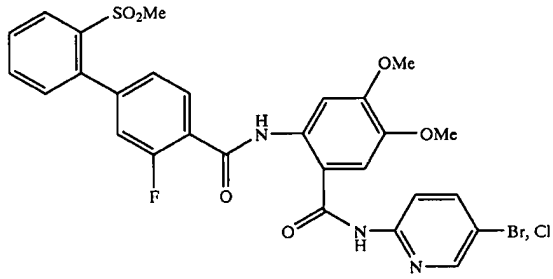

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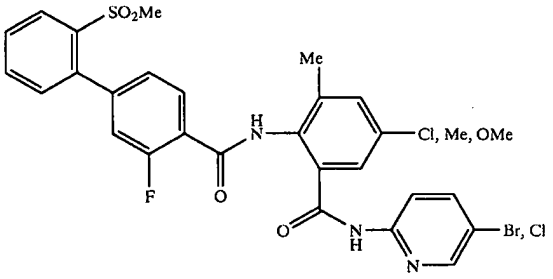

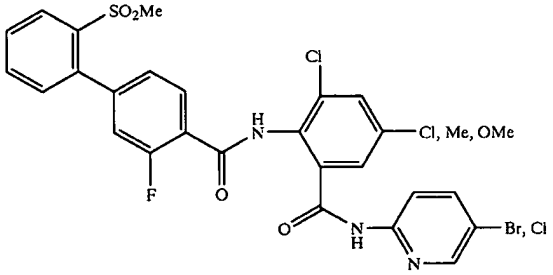

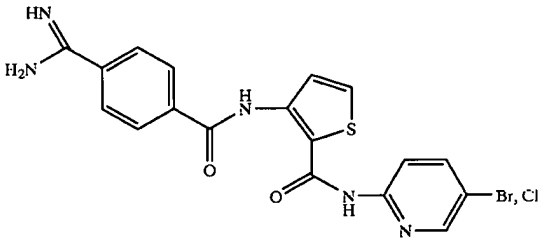

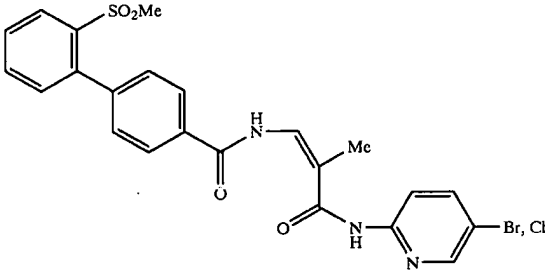

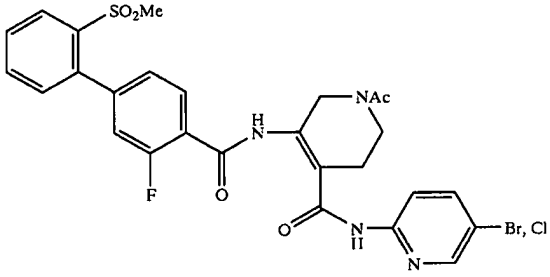

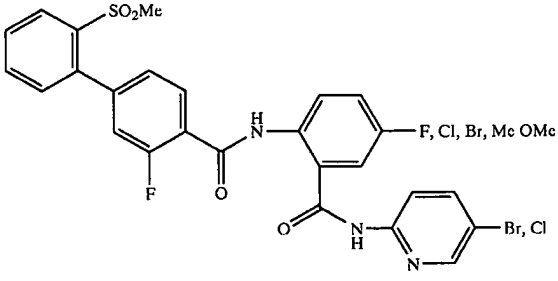

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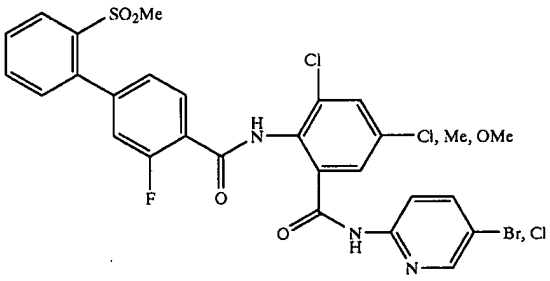
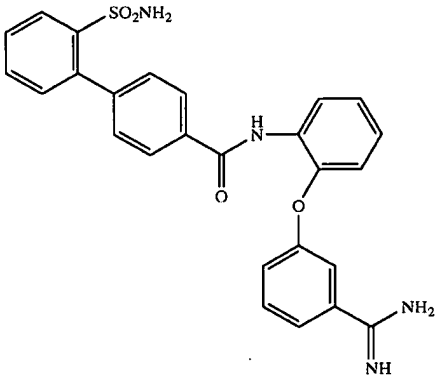
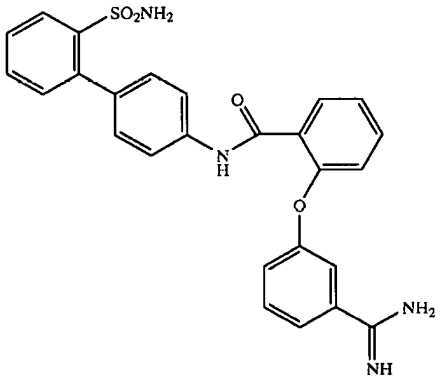
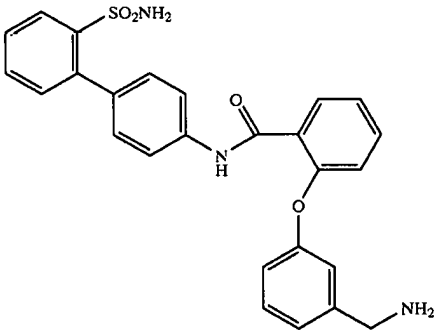


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides the following compounds:







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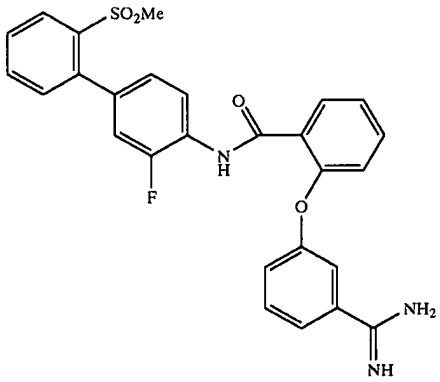

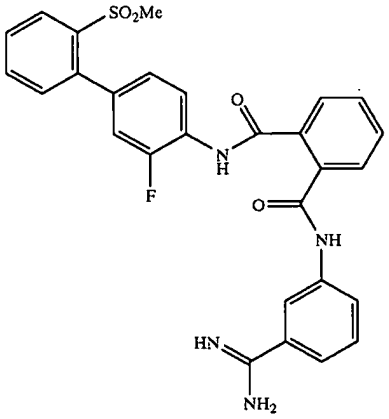

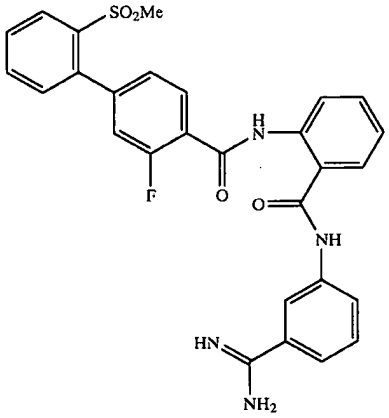

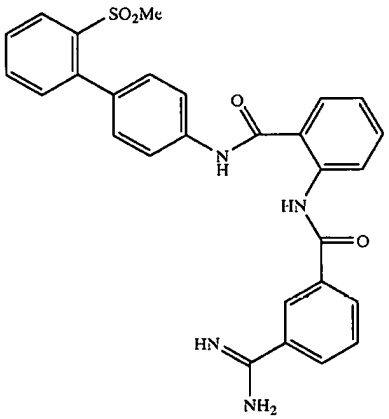

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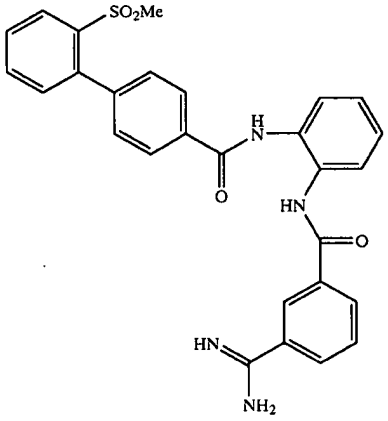

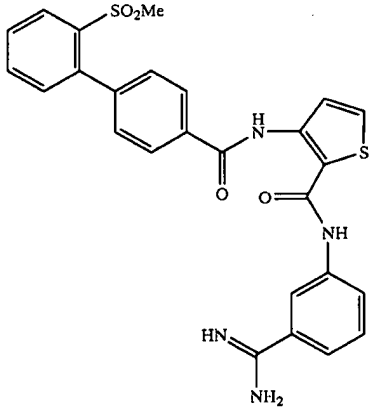

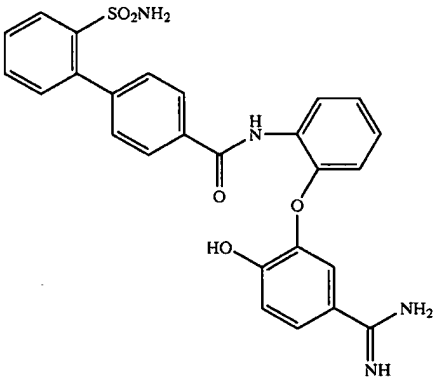

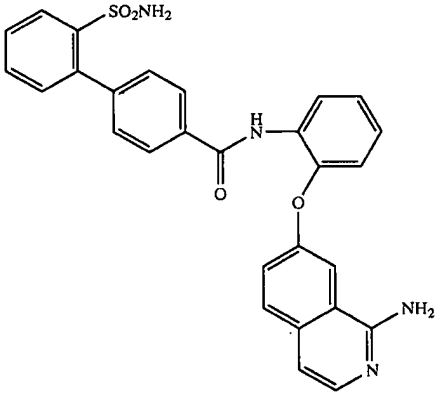

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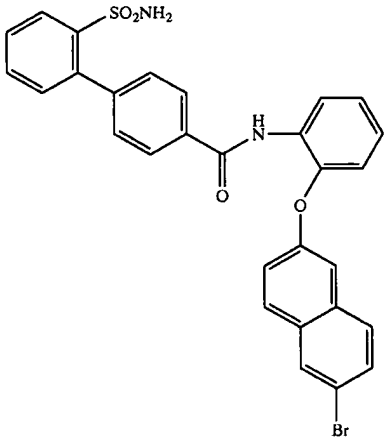

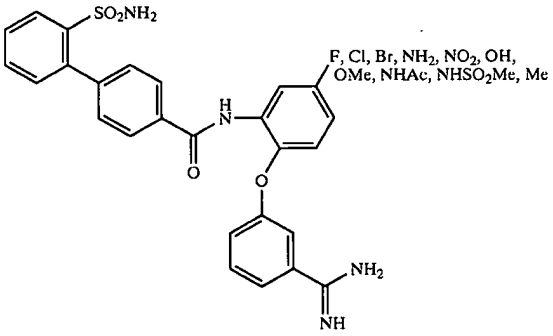

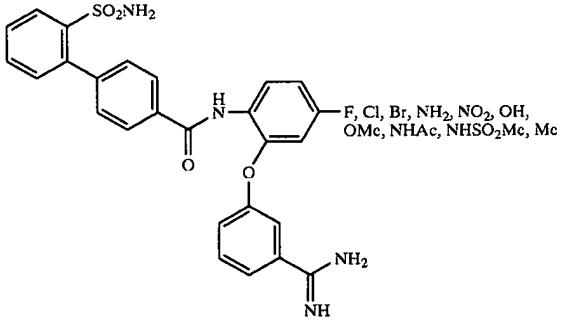

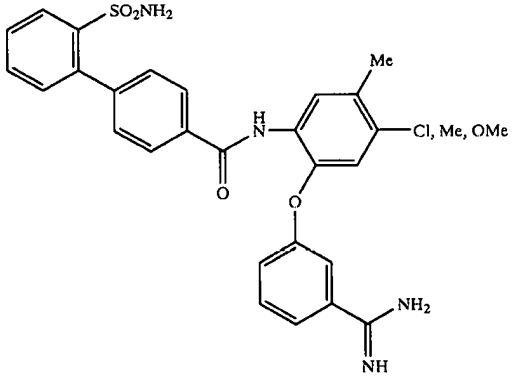

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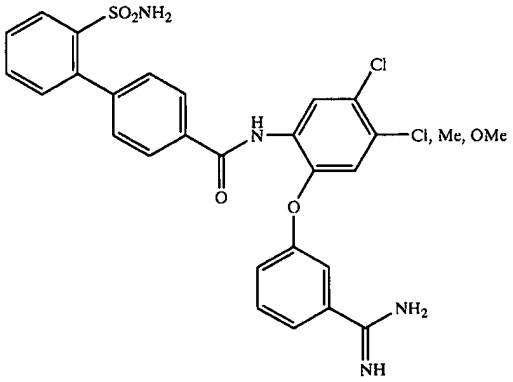
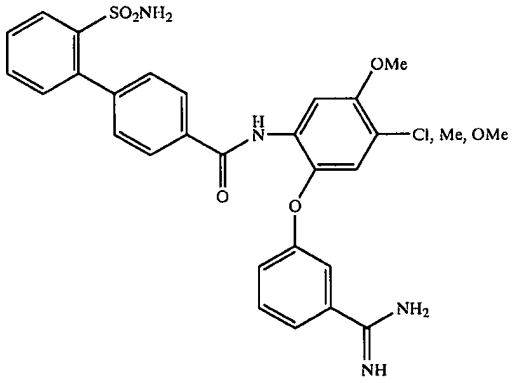
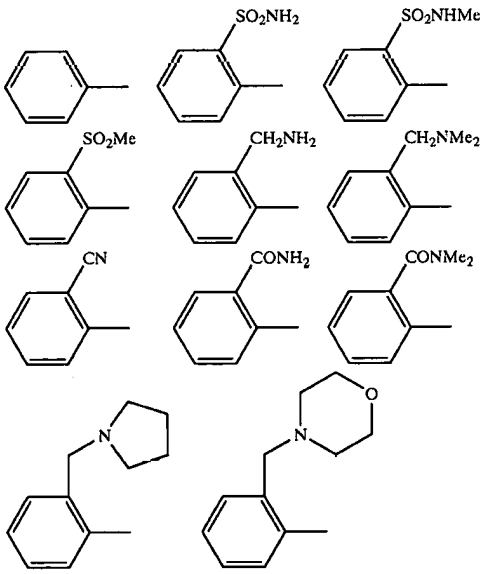




and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention also provides compounds of formula Ib, as set forth above, wherein:

A is a member selected from the group consisting of:



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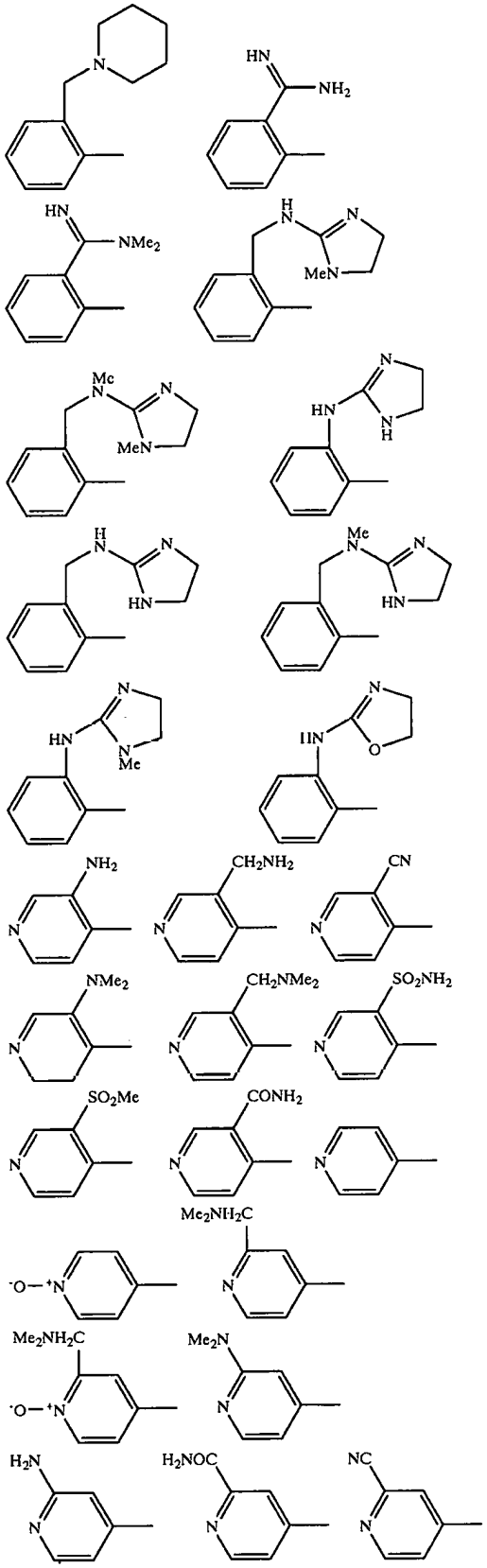

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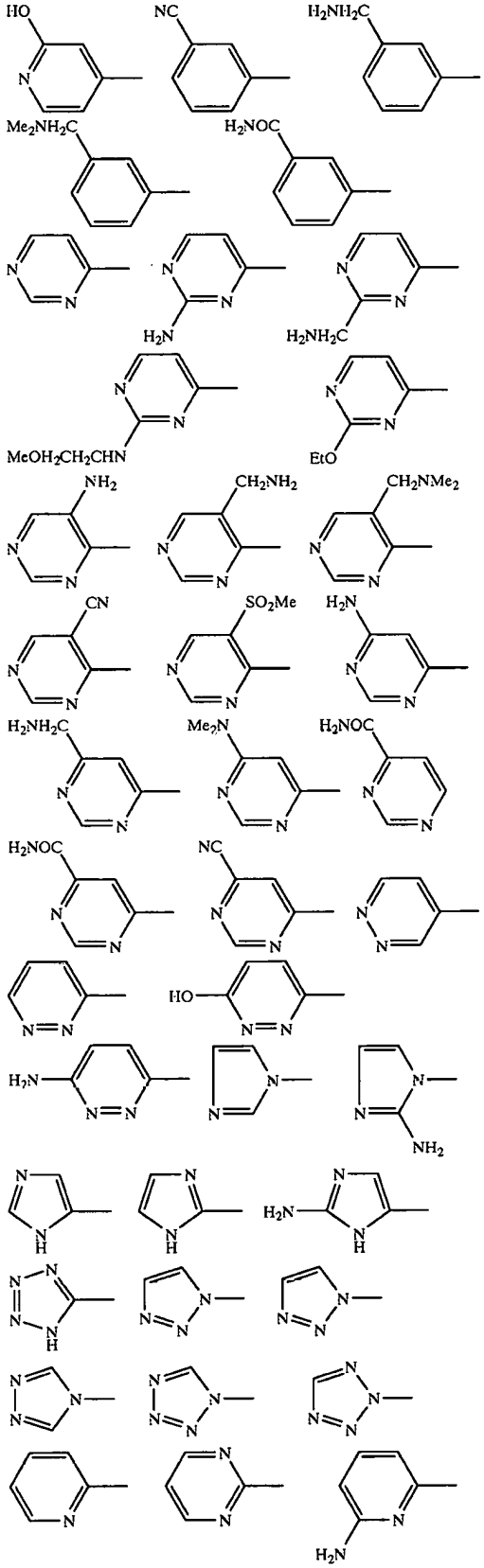

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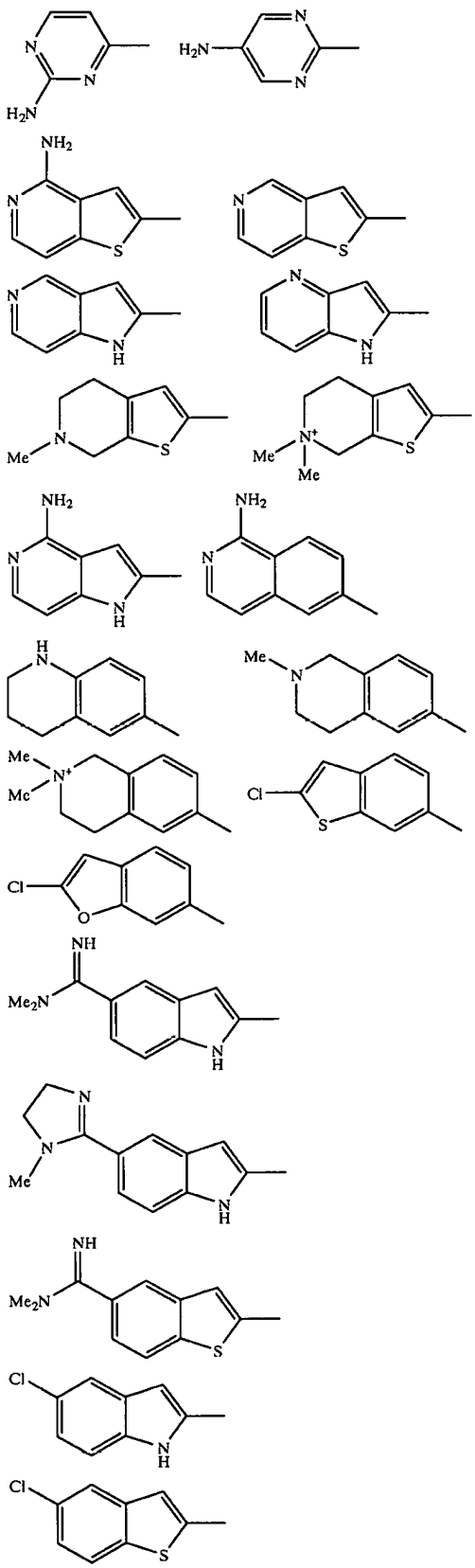

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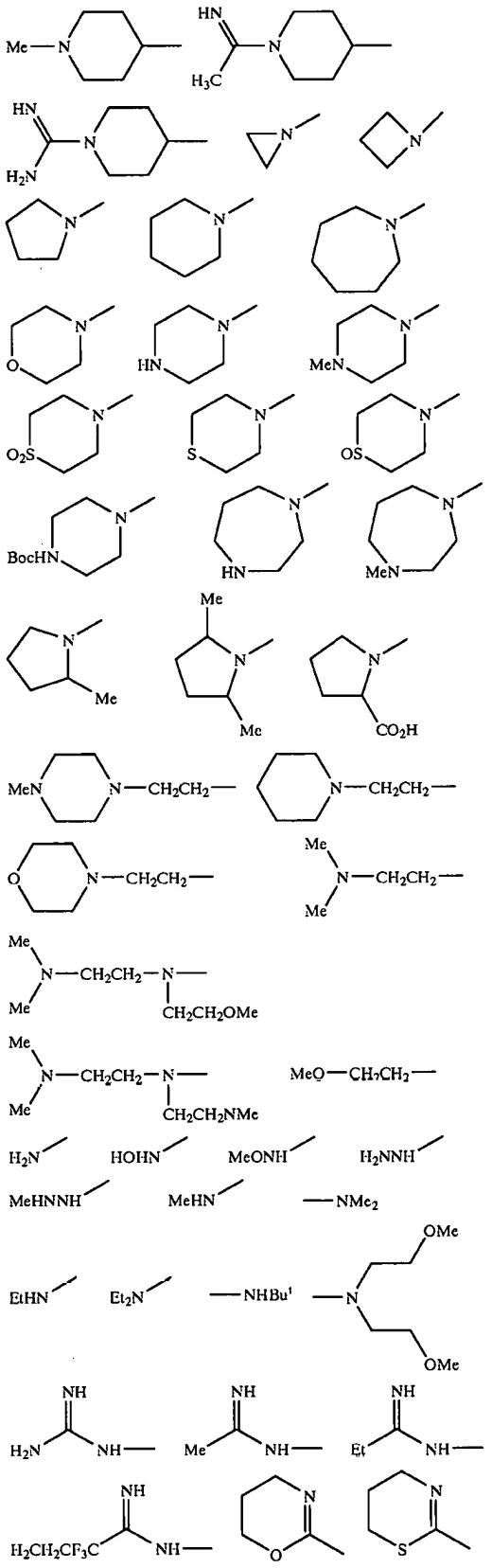

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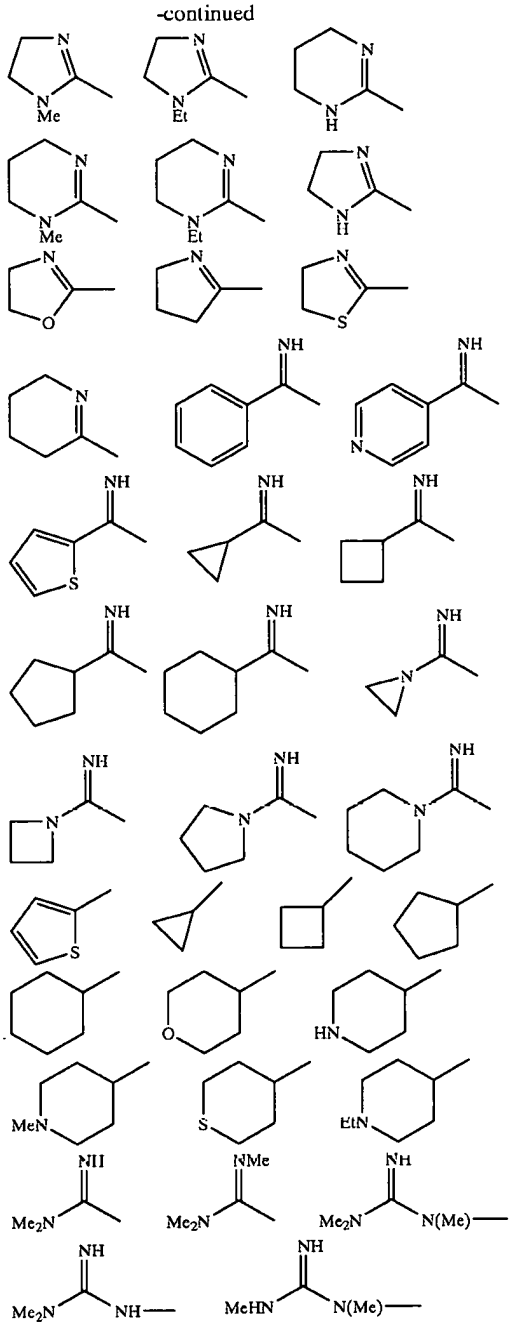
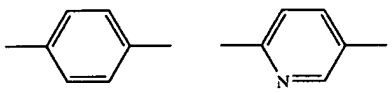


Q is a member selected from the group consisting of:

a direct link, —CH_2—, —C(=O)—, —NH—, —N(Me)—, —$NHCH_2$—, —$N(Me)CH_2$—, —C(=NH)—, —C(=NMe)—;

D is a direct link or is a member selected from the group consisting of:



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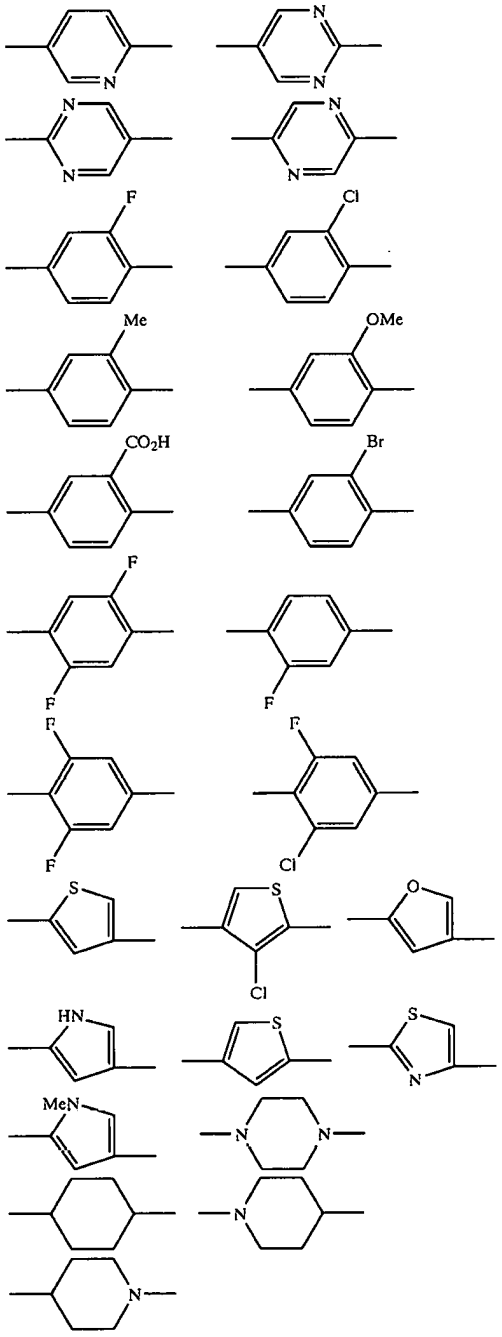

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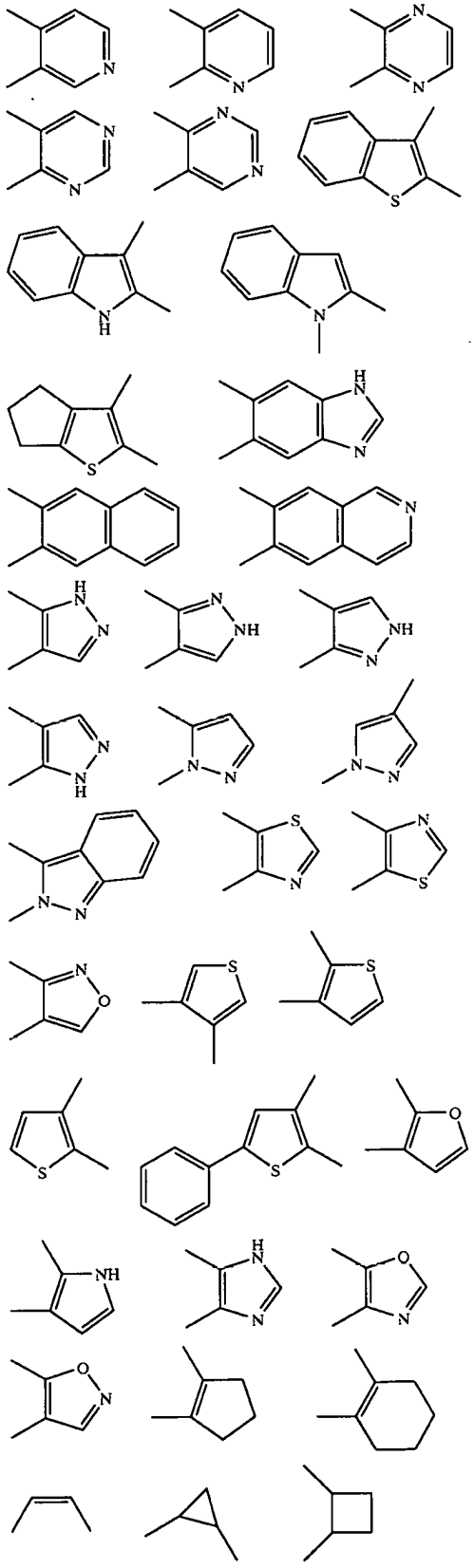
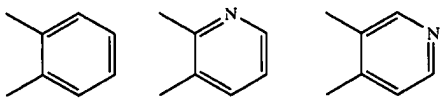


E is a member selected from the group consisting of:

a direct link, —CH_2NH—, —$NHCH_2$—, —CH_2O—, —OCH_2—, —CH_2NH—, —CONH—, —NHCO—, —CONMe—, —NMeCO—;

G is a member selected from the group consisting of:



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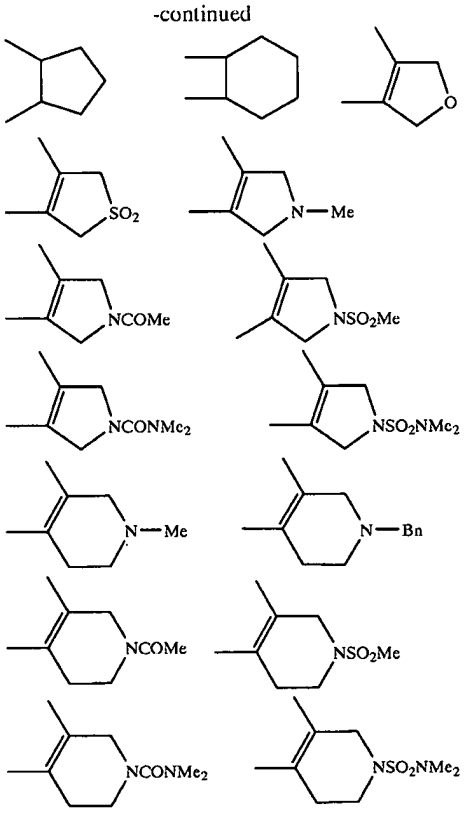

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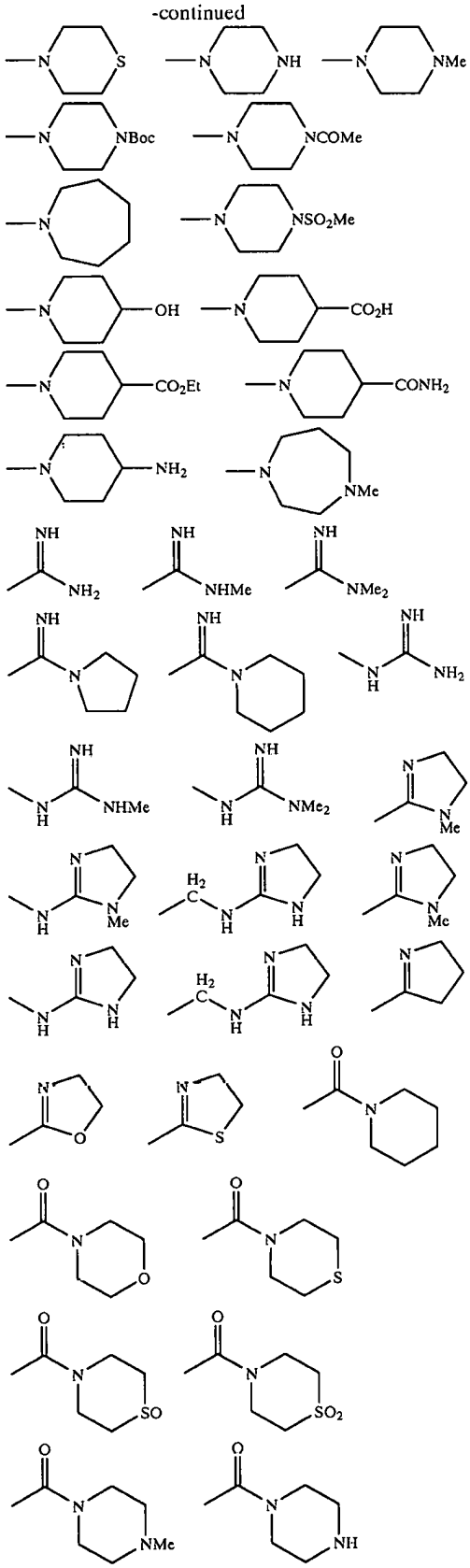
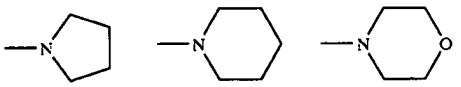


G is substituted by 0–4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —NHCH2CONHMe, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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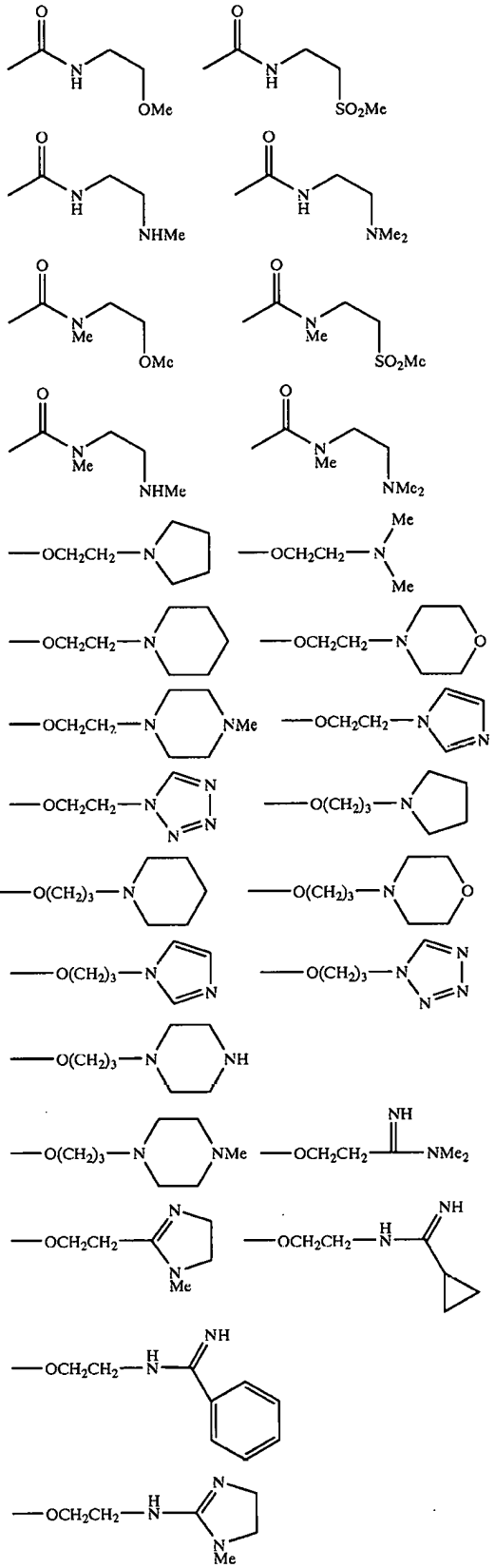

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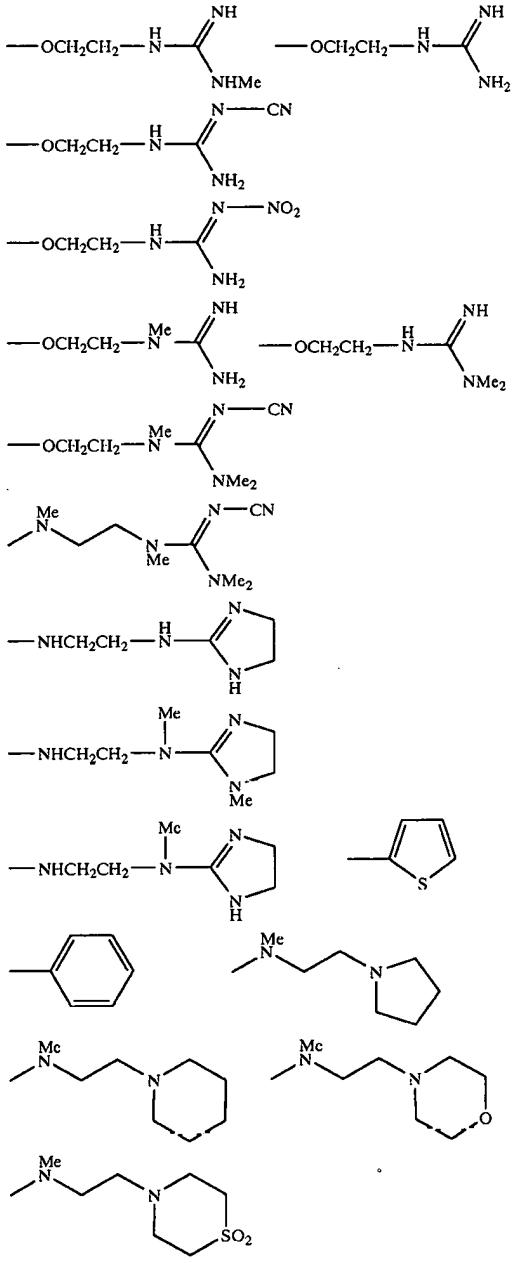
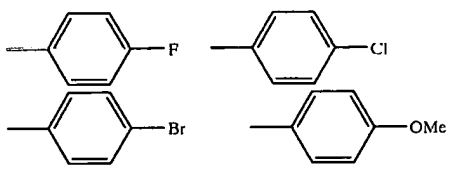


J is a member selected from the group consisting of:

a direct link, —SO2—, —CO—, —O—, —NH—, —C(=O)—NH— and —NH—C(=O)—;

X is a member selected from the group consisting of:



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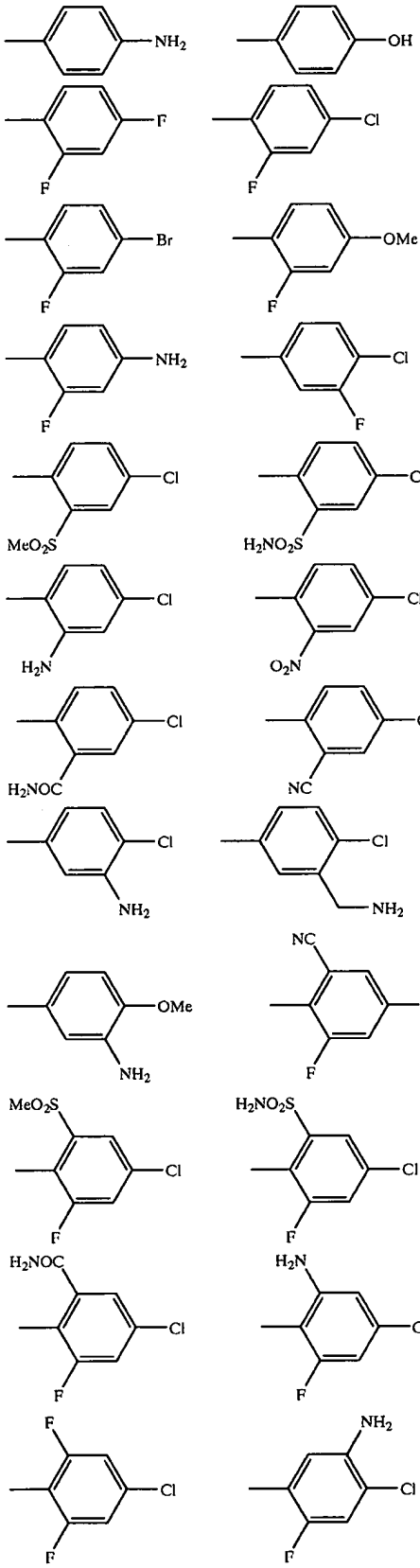

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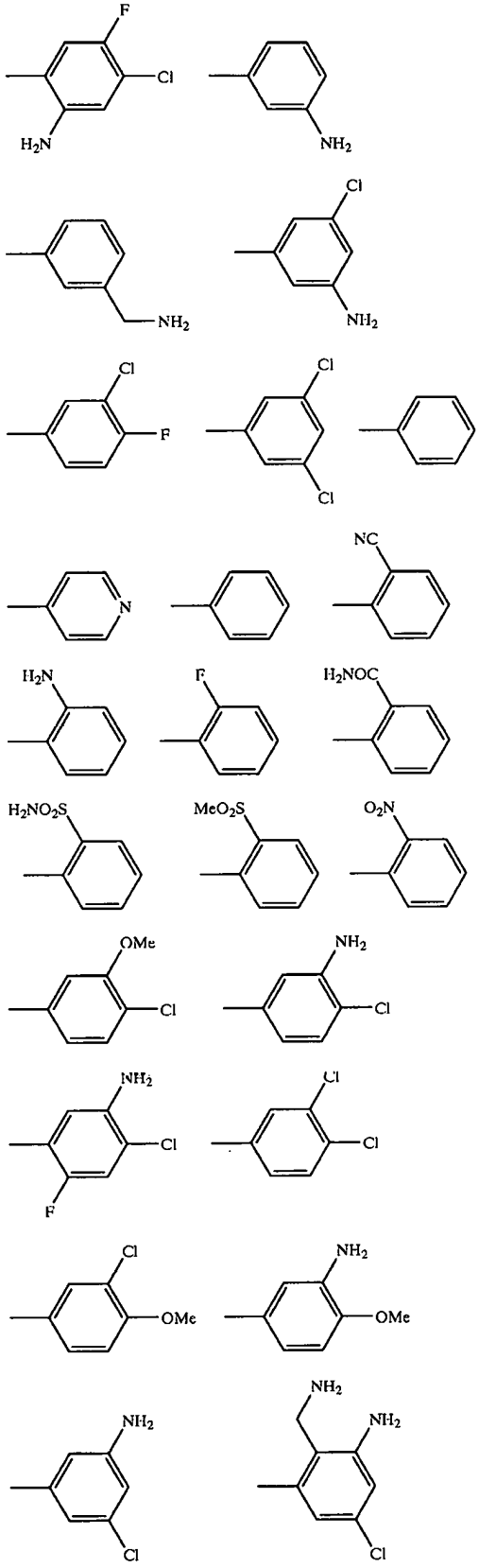

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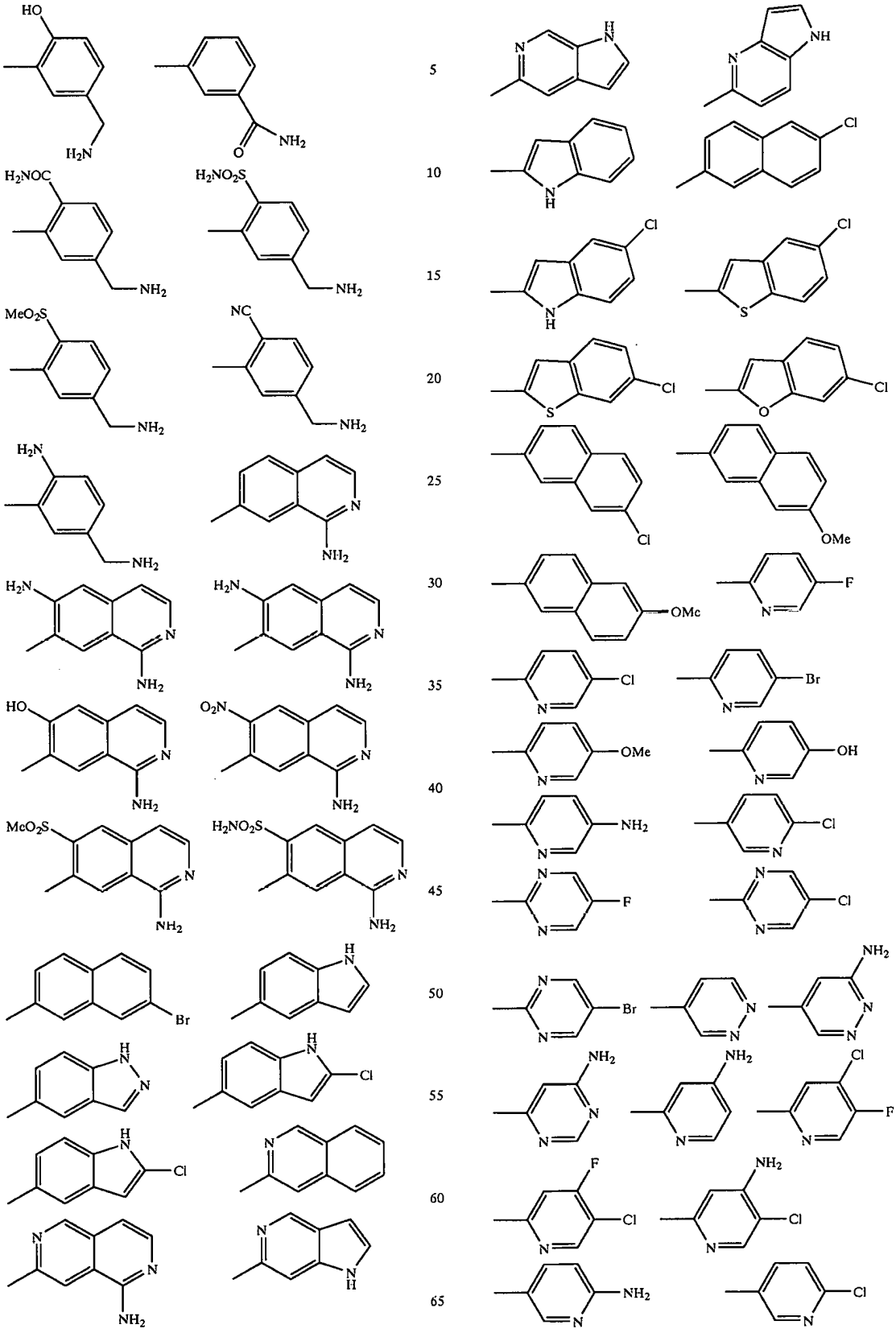

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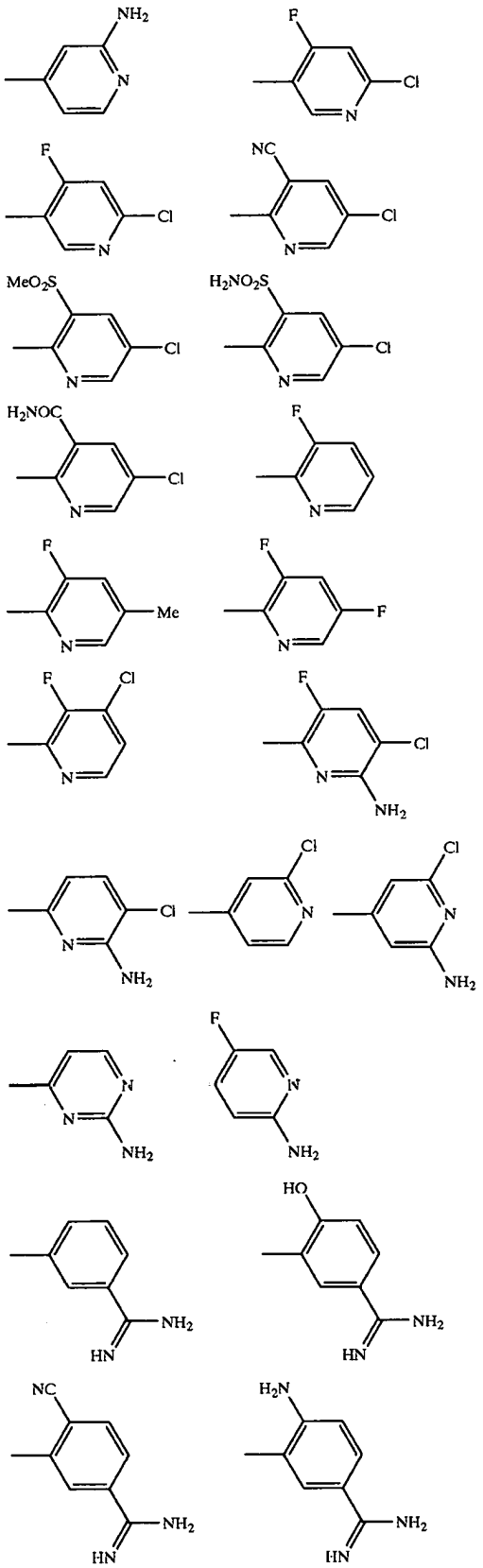

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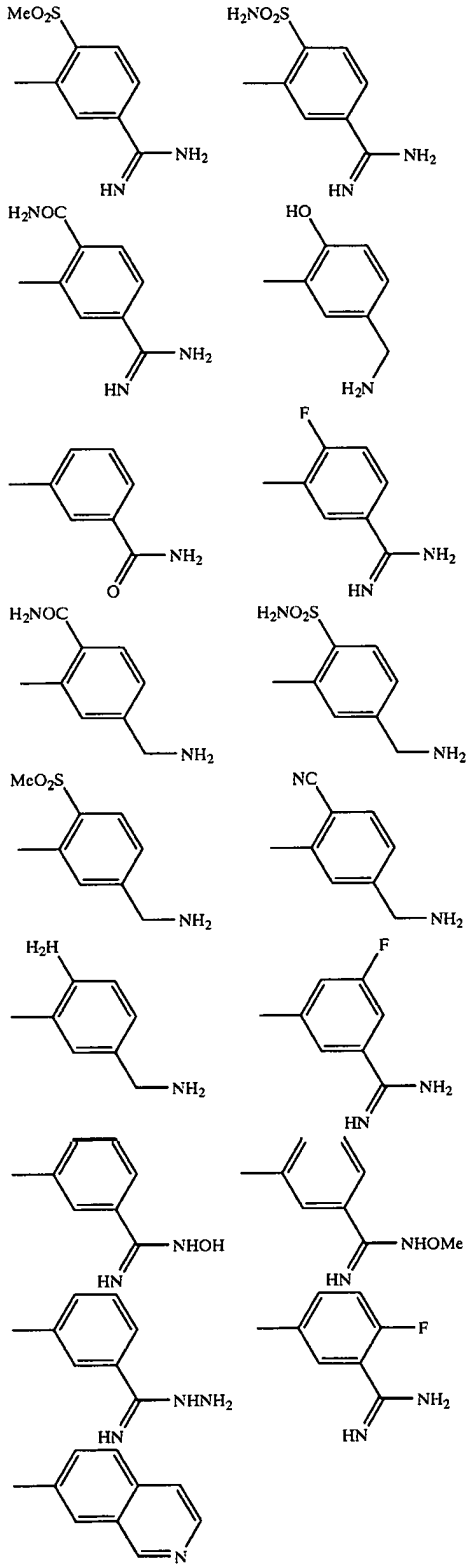
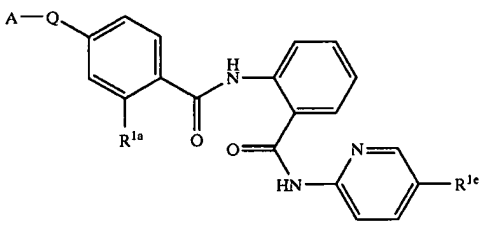


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



where:

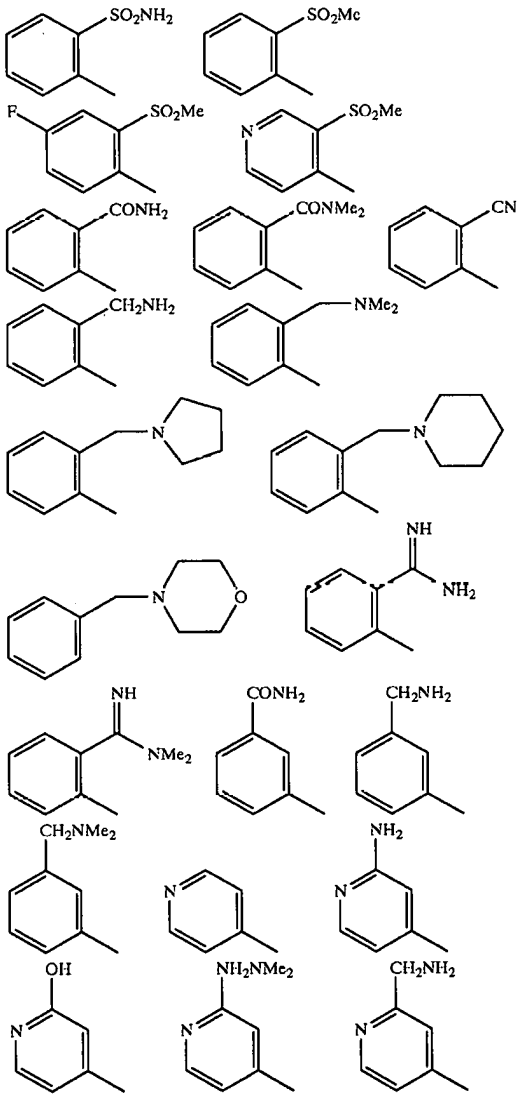
R^{1a} is a member selected from the group consisting of:

H, —F, —Cl and —Br;

R^{1e} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; and

A-Q is a member selected from the group consisting of:



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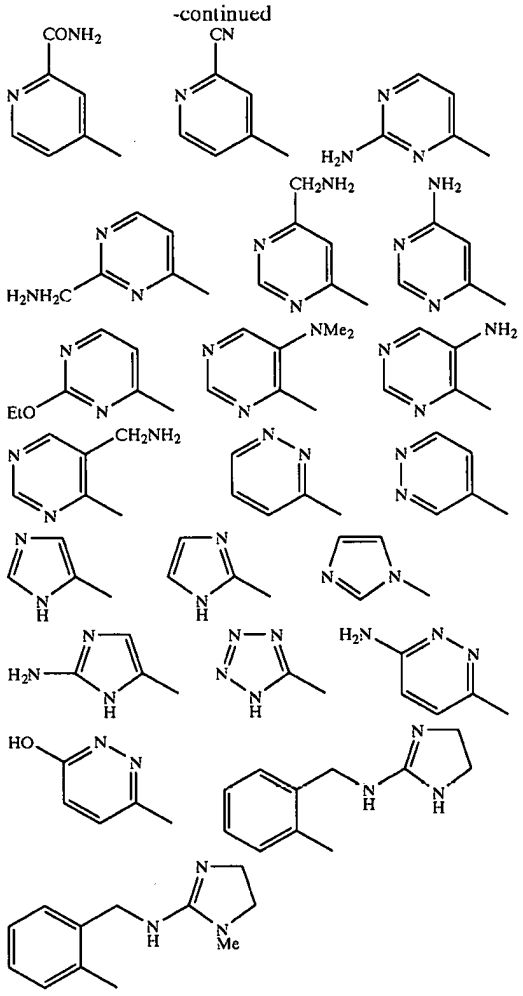
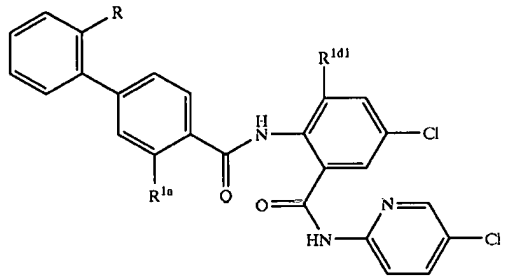


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, having the following structure:



wherein:

R is a member selected from the group consisting of:

—SO_2Me, —SO_2NH_2, —CH_2NH_2, —$CH_2N(CH_3)_2$;

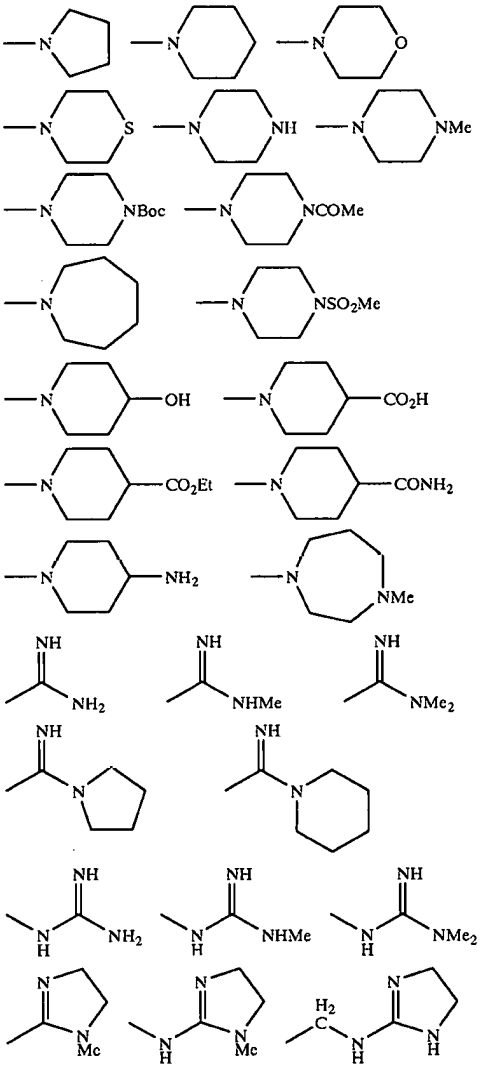
R^{1a} is a member selected from the group consisting of:

H, —F;

R^{1d1} is a member selected from the group consisting of:

H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe,

—CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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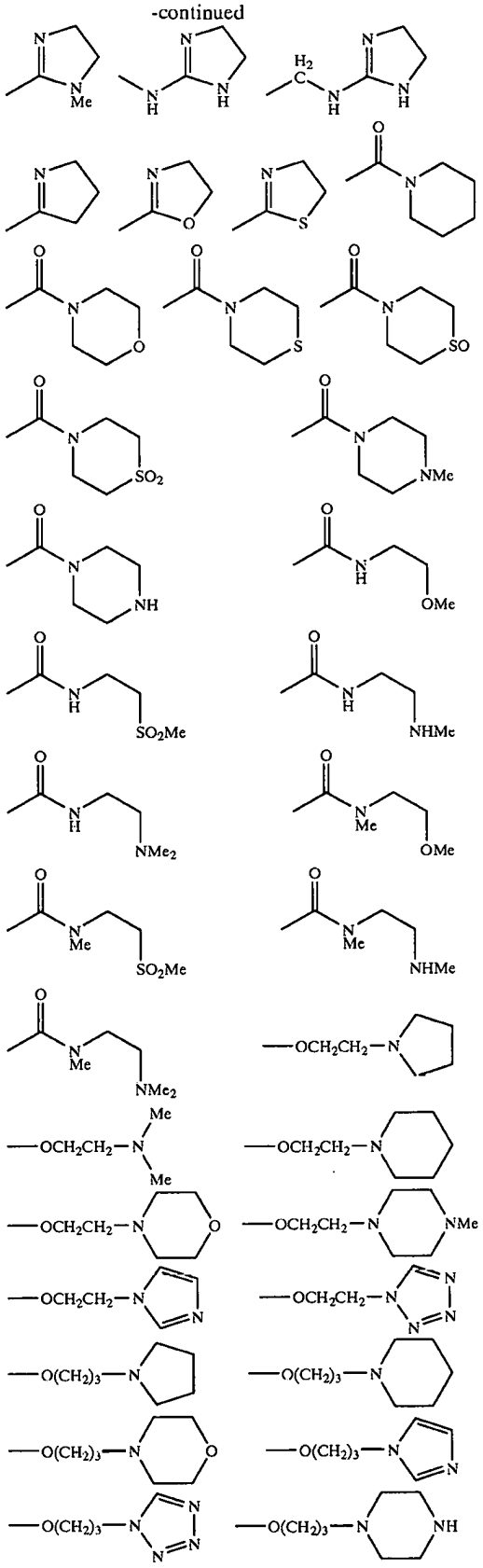

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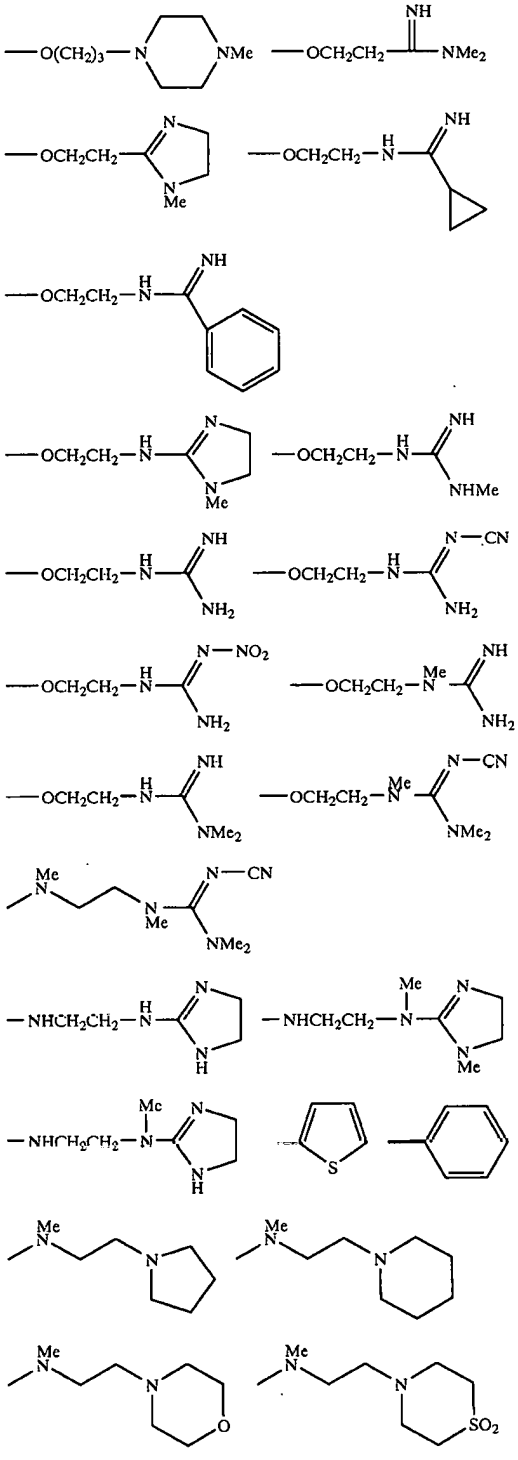
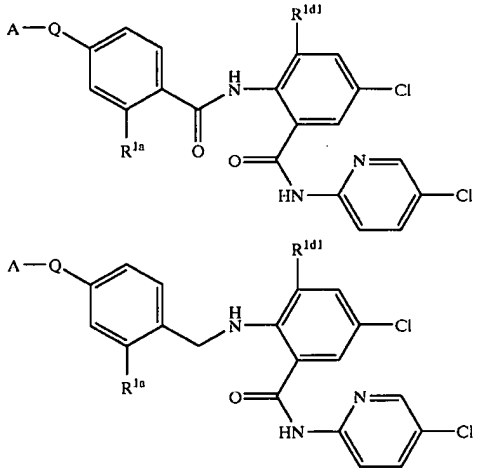


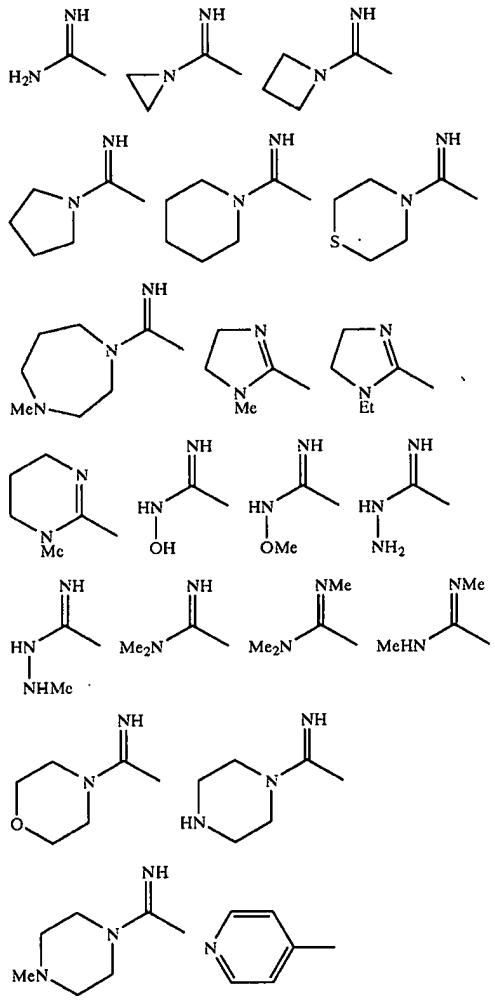
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



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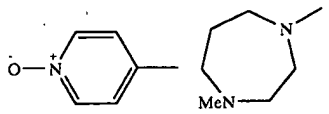
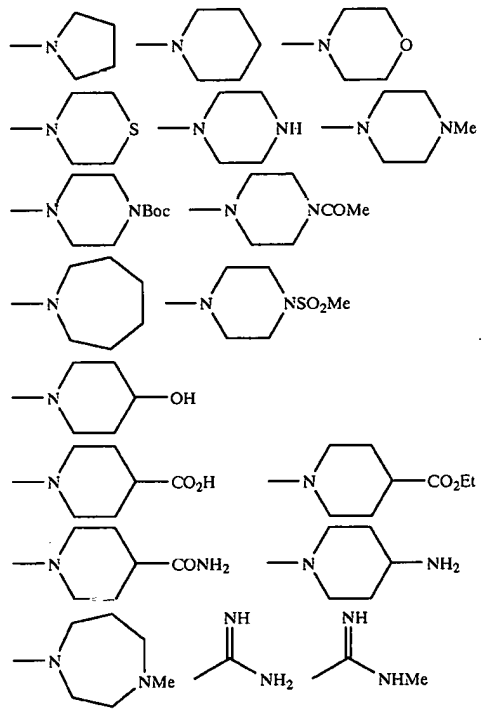


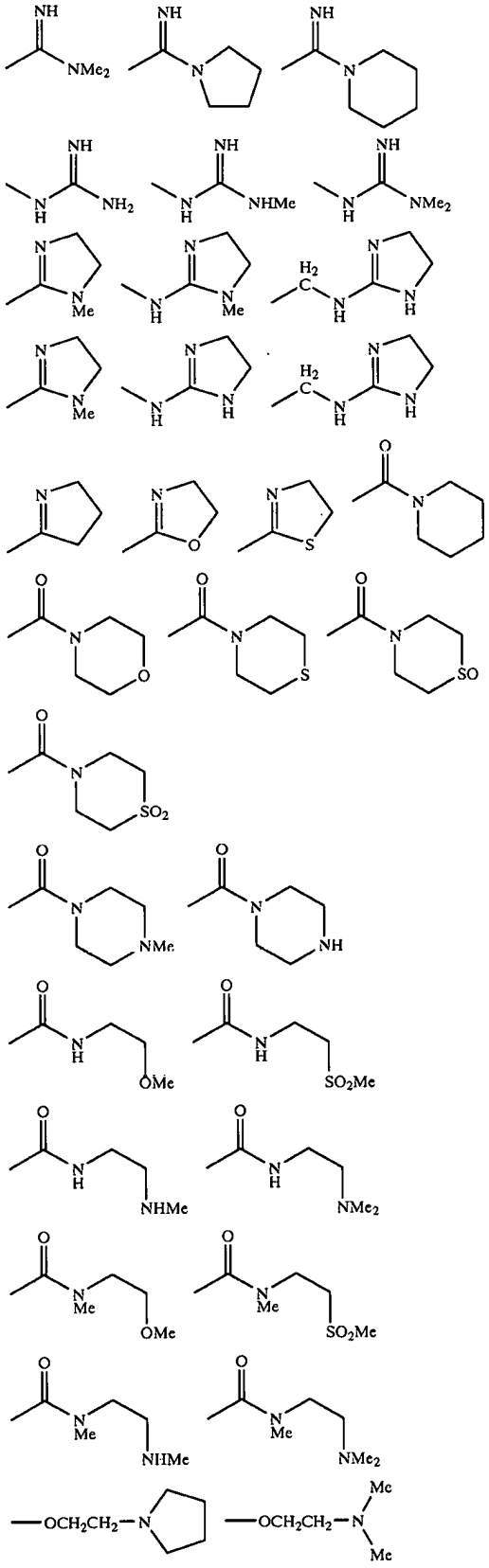
R^{1a} is a member selected from the group consisting of:

H, —F;

R^{1d1} is a member selected from the group consisting of:

H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2Me, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2ROMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,





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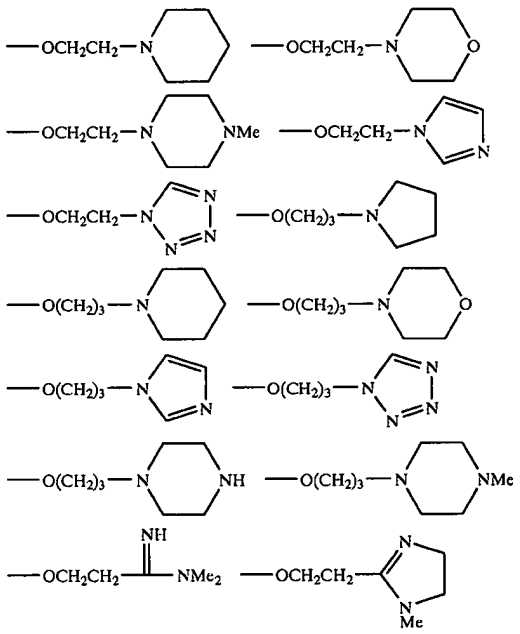

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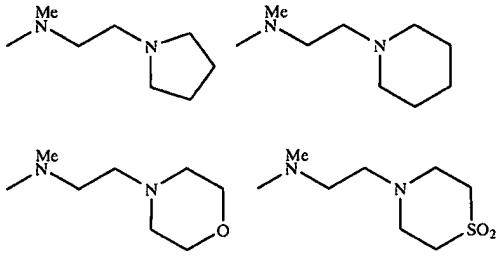
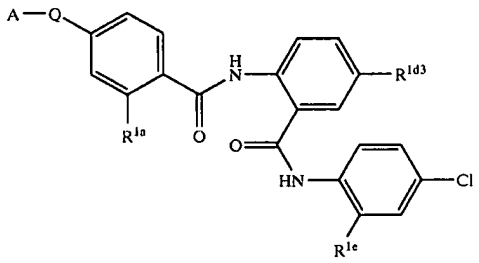
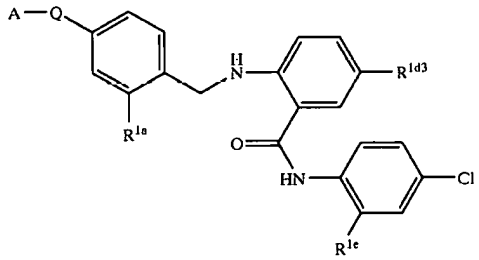


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

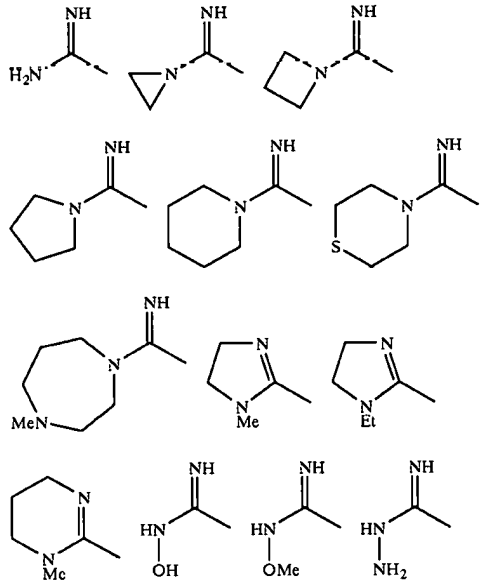
The invention provides compound of formula Ib, as described above, having the following structure:





wherein:

A-Q is a member selected from the group consisting of:



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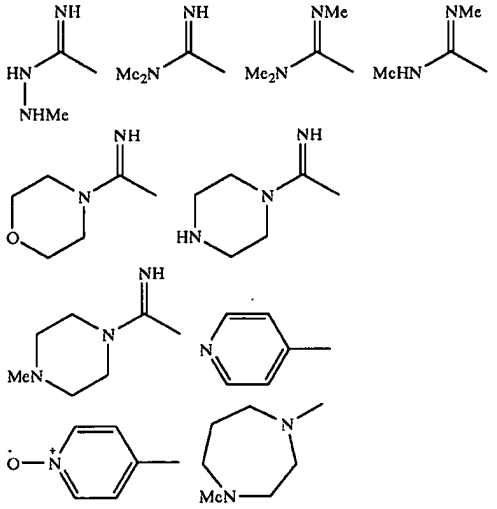

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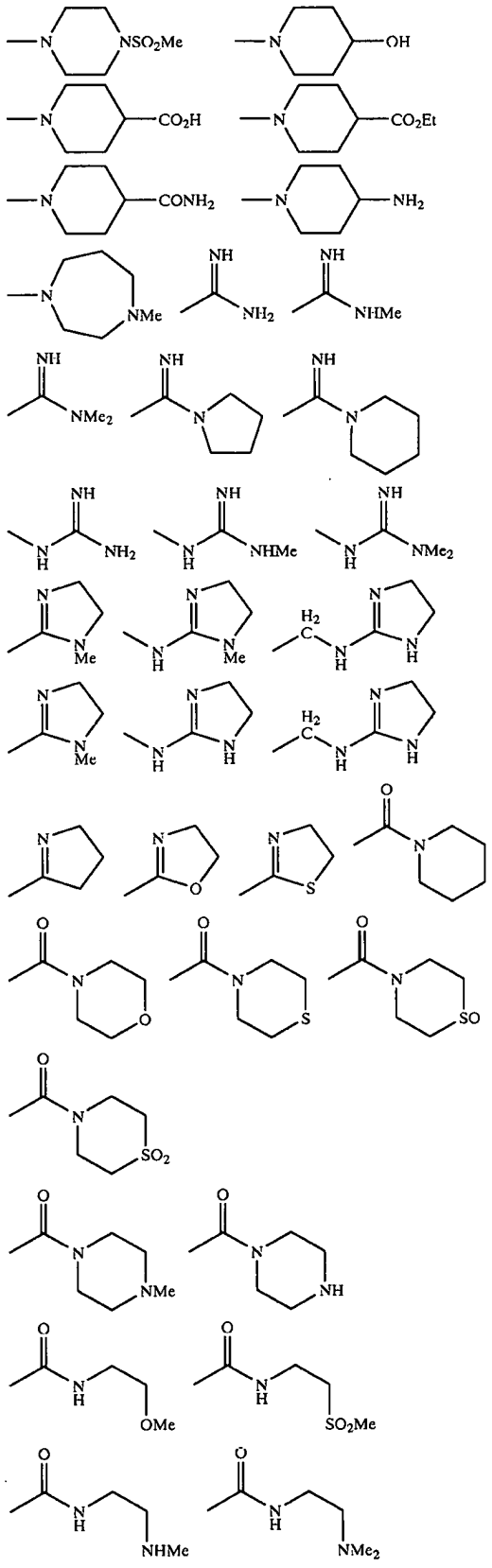


R^{1a} is a member selected from the group consisting of:

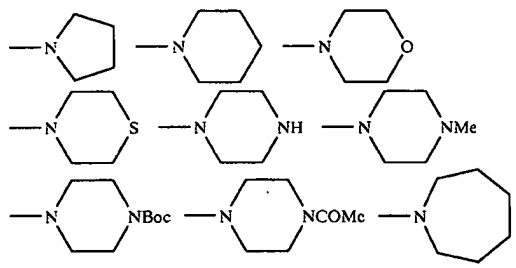
H, —F;

R^{1e} is a member selected from the group consisting of:

H, —F, —SO_2Me, —SO_2NH_2, —CN, —$CONH_2$, —CH_2NH_2, —CH_2NMe_2;

R^{1d3} is a member selected from the group consisting of:

H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH_2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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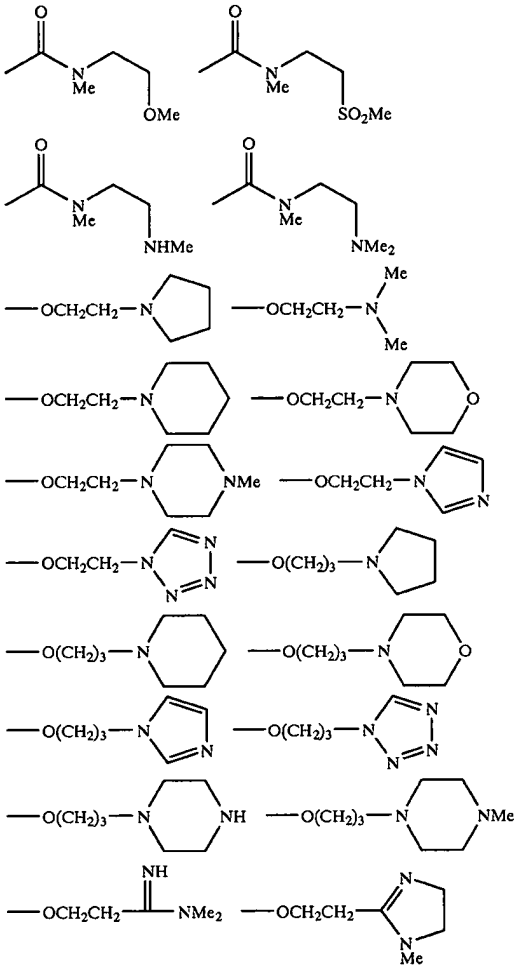

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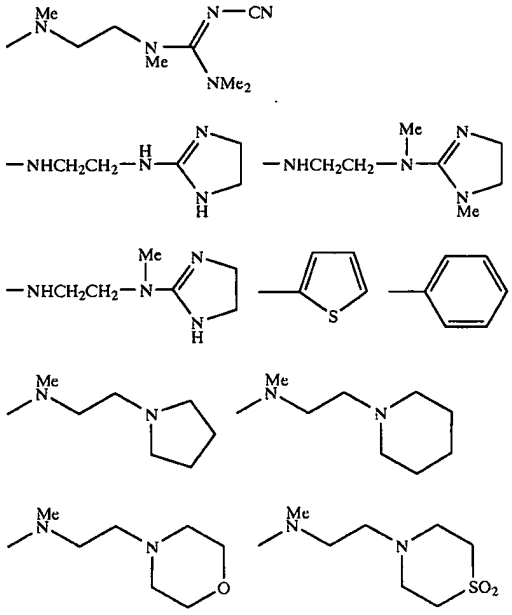
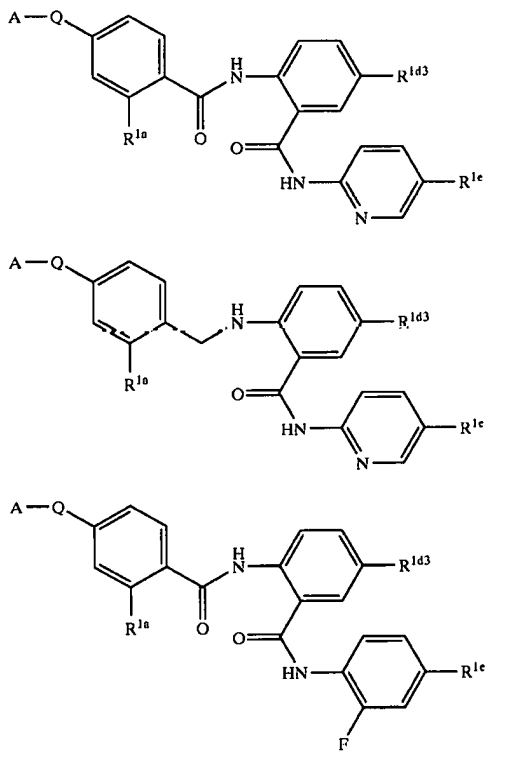


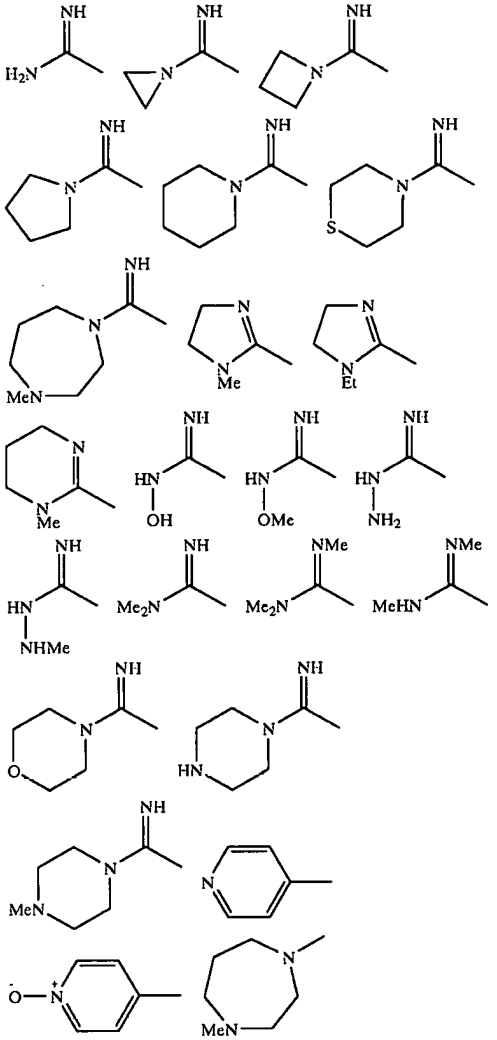
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

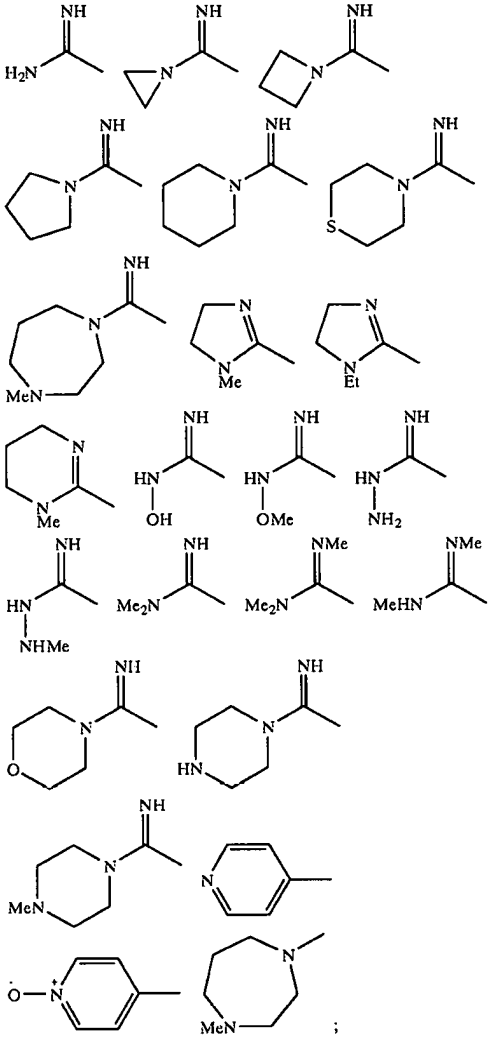
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:





R^{1a} is a member selected from the group consisting of:

H, —F;

R^{1e} is a member selected from the group consisting of:

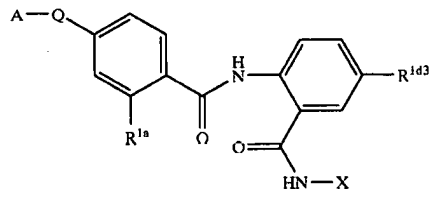
—Cl, —Br;

R^{1d3} is a member selected from the group consisting of:

H, F, Cl, Br, —OCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:

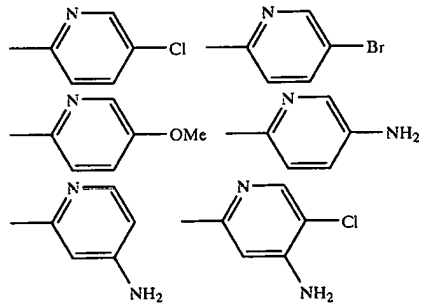
R^{1a} is a member selected from the group consisting of:

H, —F;

R^{1d3} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —$NHSO_2Me$, —NHAc, —SO_2Me, —SO_2NH_2;

X is a member selected from the group consisting of:



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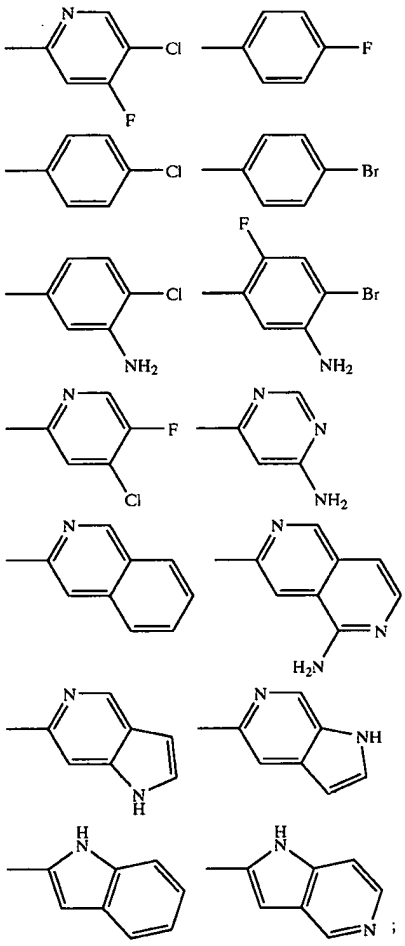
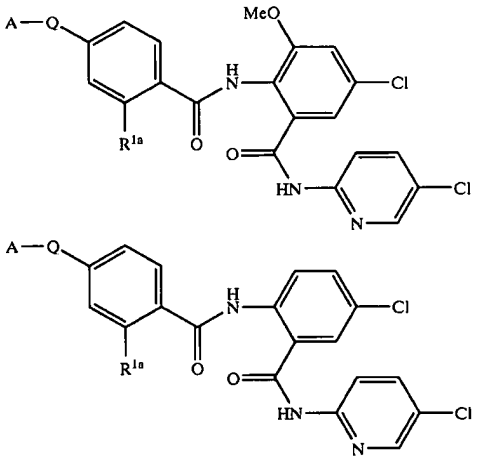


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



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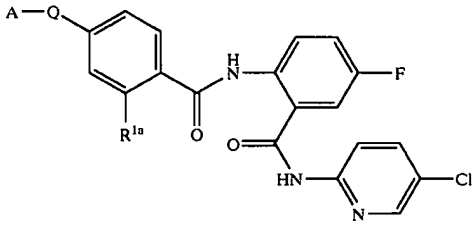
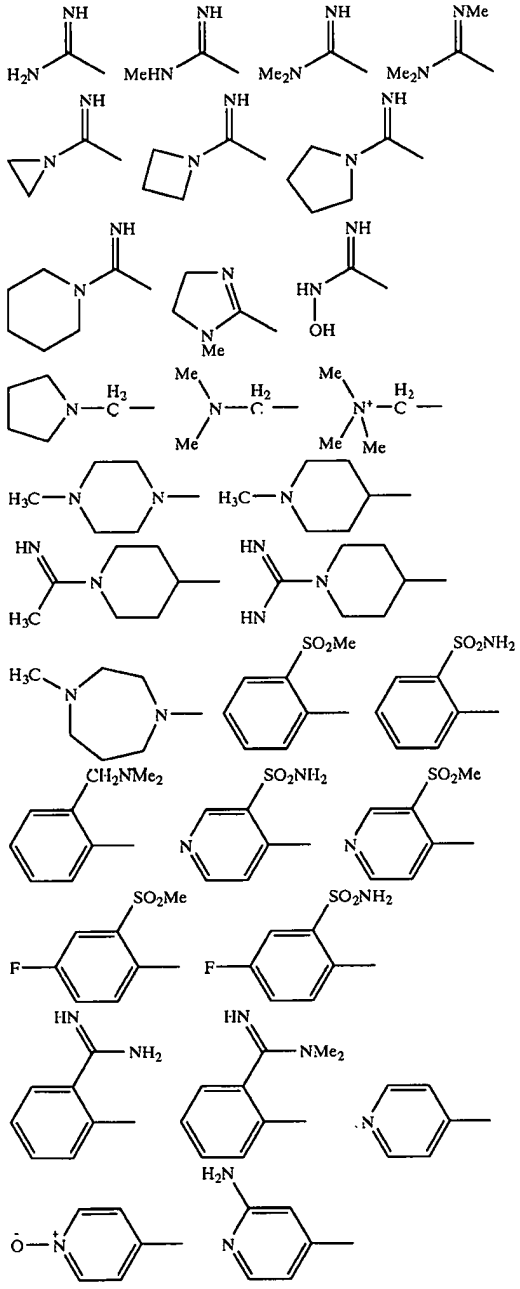


wherein:

A-Q is a member selected from the group consisting of:



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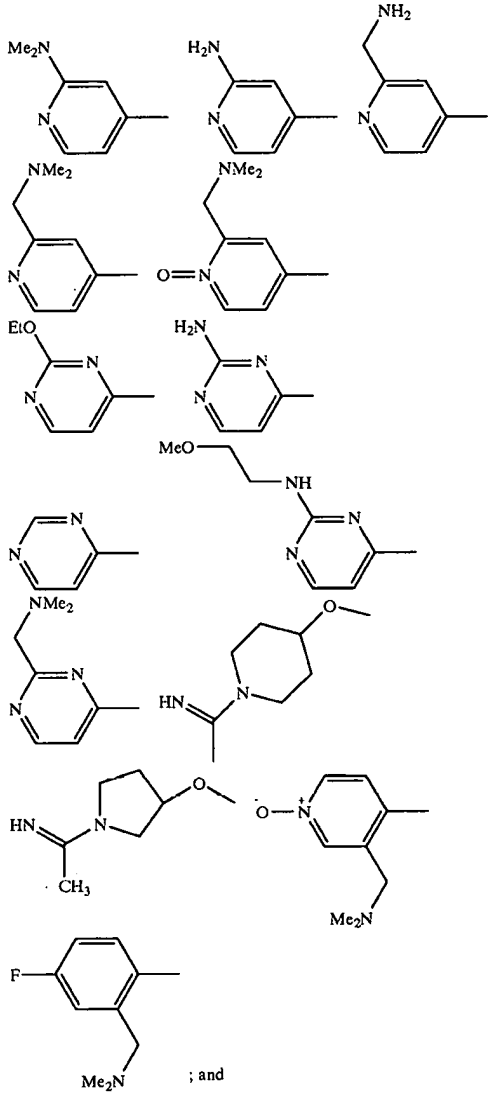


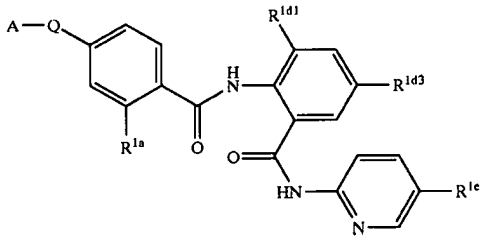
; and

R^{1a} is a member selected from the group consisting of:

H, —F;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is a member selected from the group consisting of:

H, —F;

R^{1d1} is a member selected from the group consisting of:

H, —OMe;

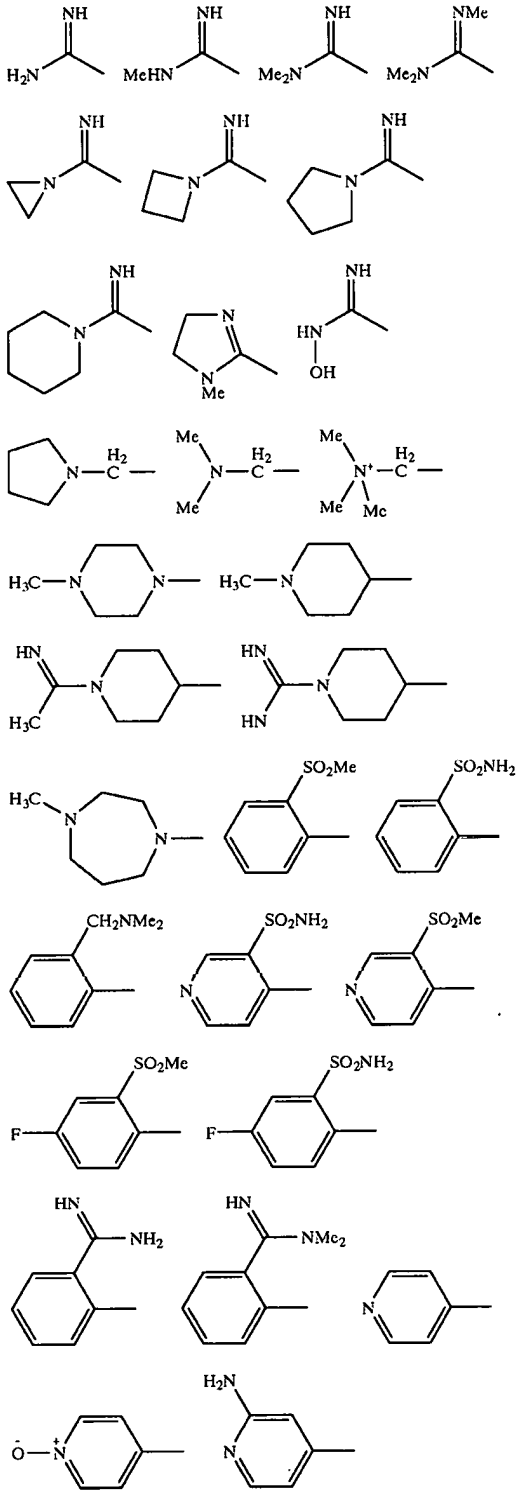
R^{1d3} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OCF_3;

R^{1e} is a member selected from the group consisting of:

H, —F, —Cl, —Br;

A-Q is a member selected from the group consisting of:



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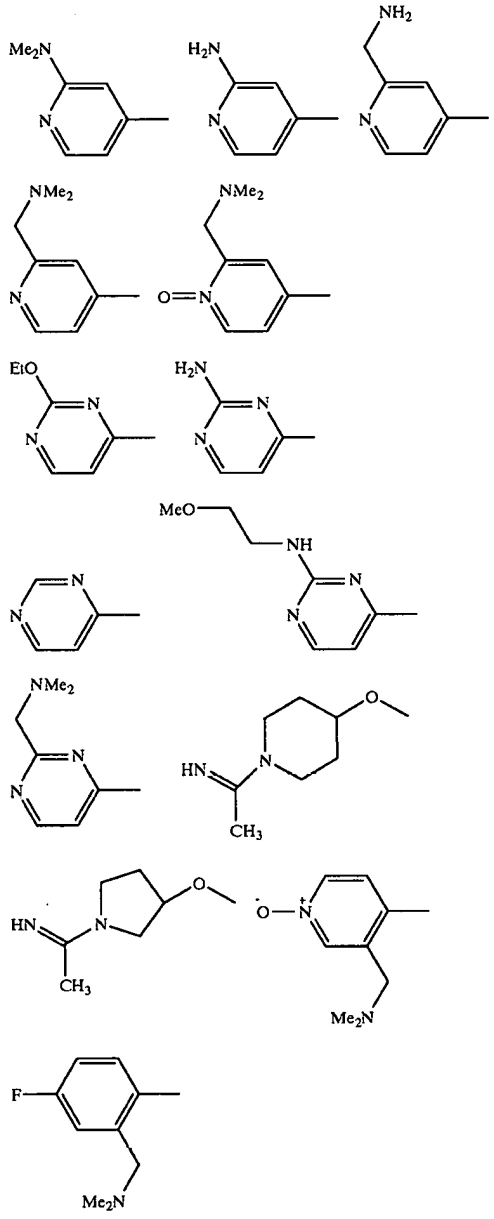
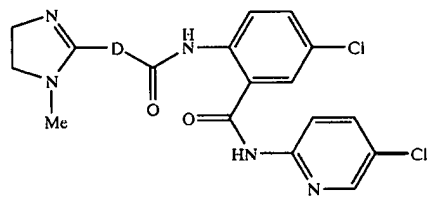


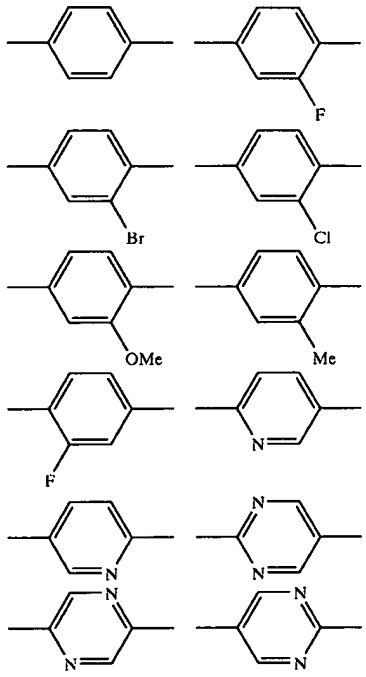
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



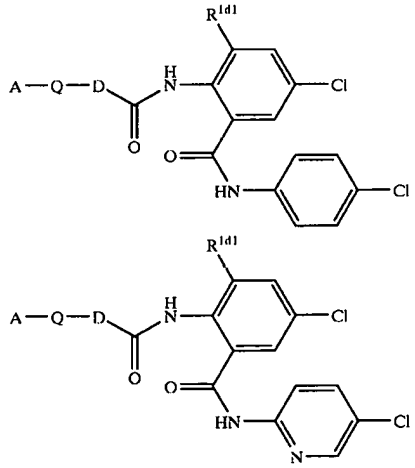
wherein:

D is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

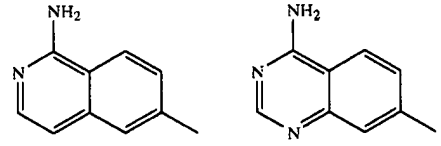
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1d1} is H or —OMe;

A-Q-D is a member selected from the group consisting of:



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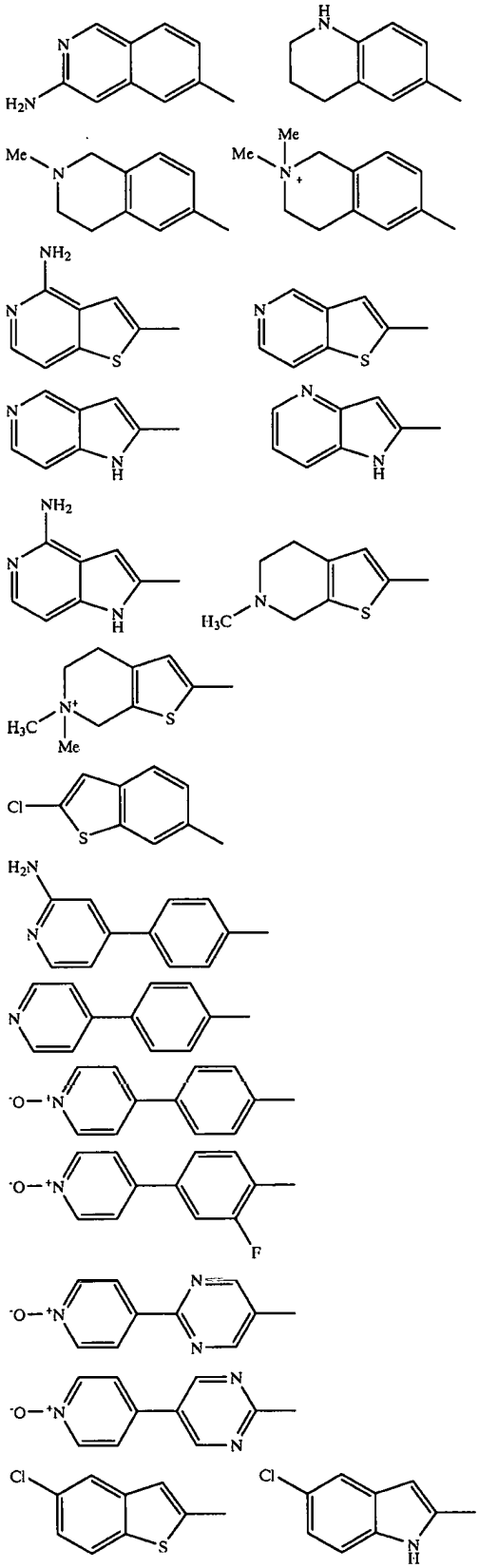

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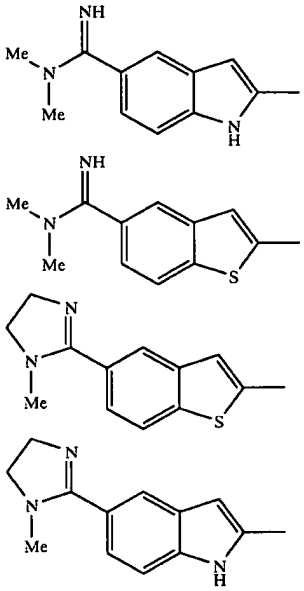
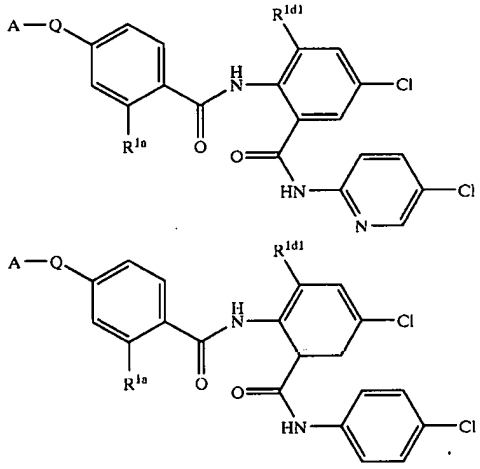


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

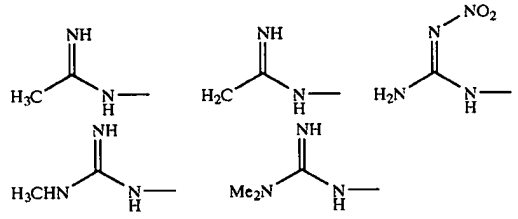


wherein:

R^{1a} is H or F;

R^{1d1} is H or —OMe;

A-Q is a member selected from the group consisting of:



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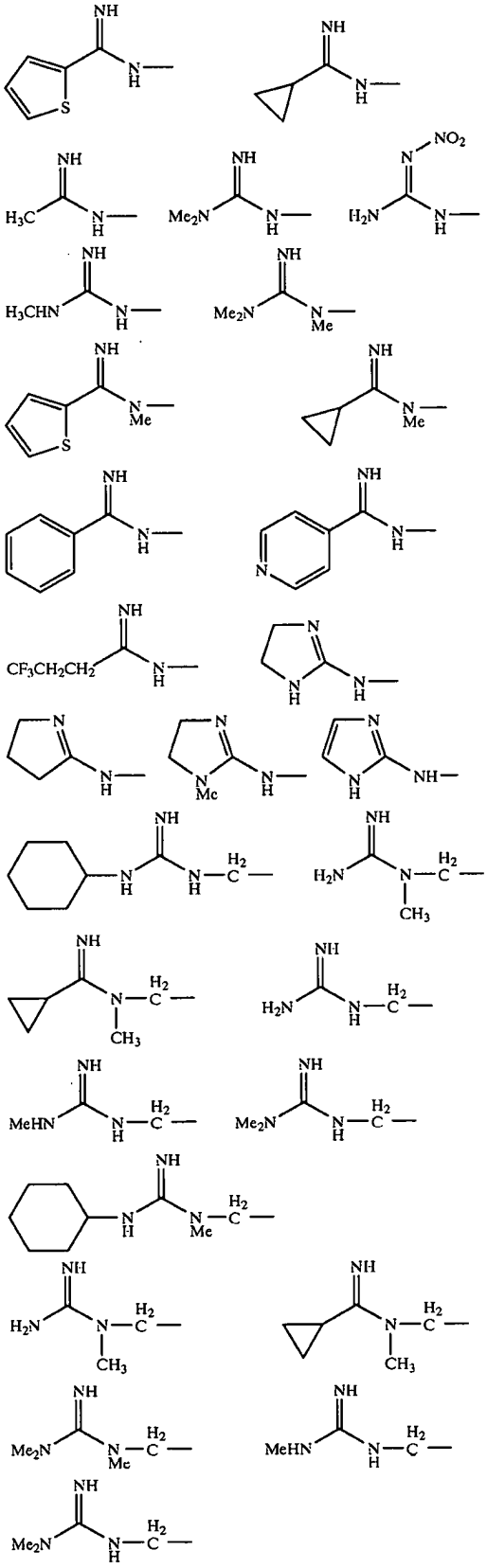

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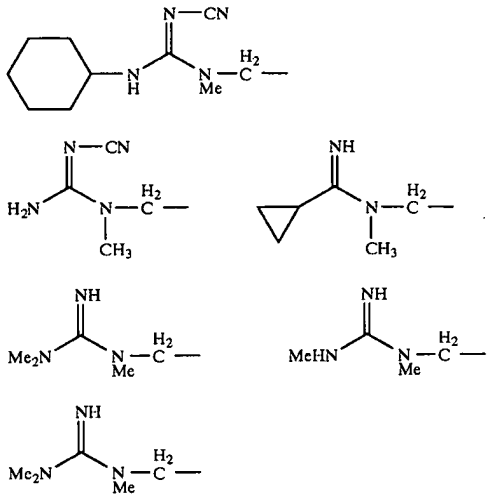
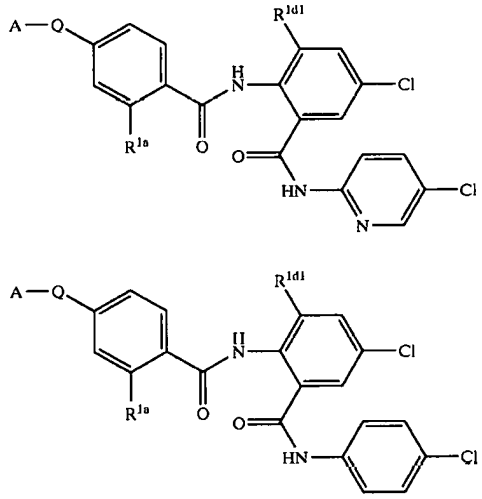


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

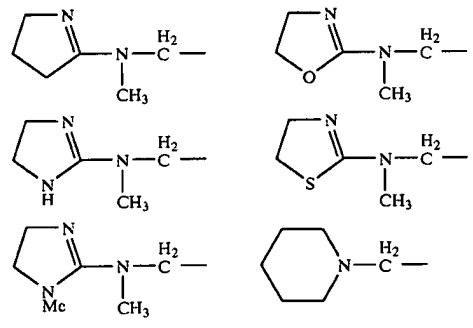


wherein:

R^{1a} is H or F;

R^{1d1} is H or —OMe;

A-Q is a member selected from the group consisting of:



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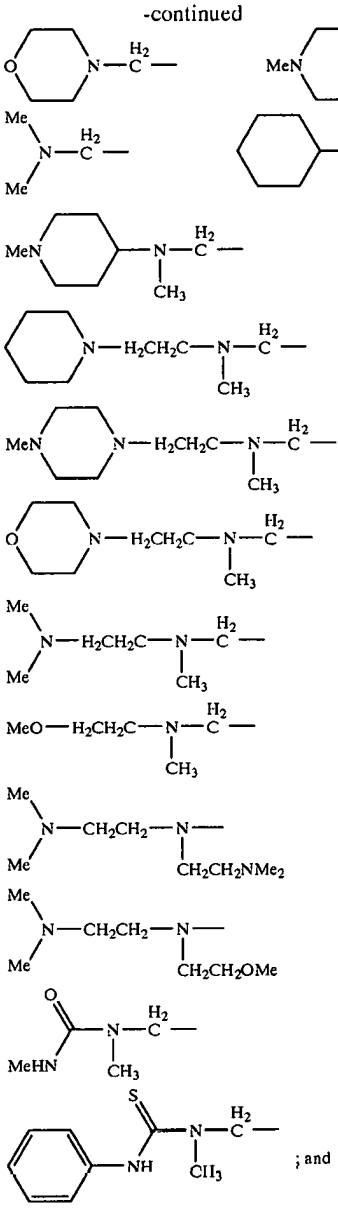
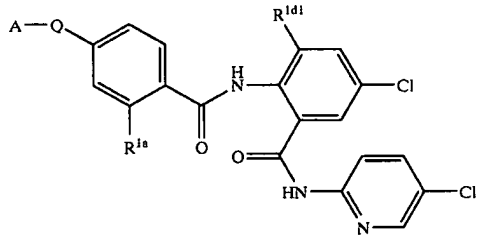


; and

R^{1a} is a member selected from the group consisting of: H, —F, and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



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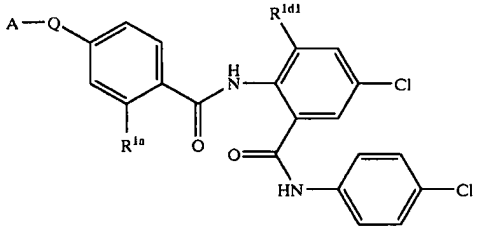
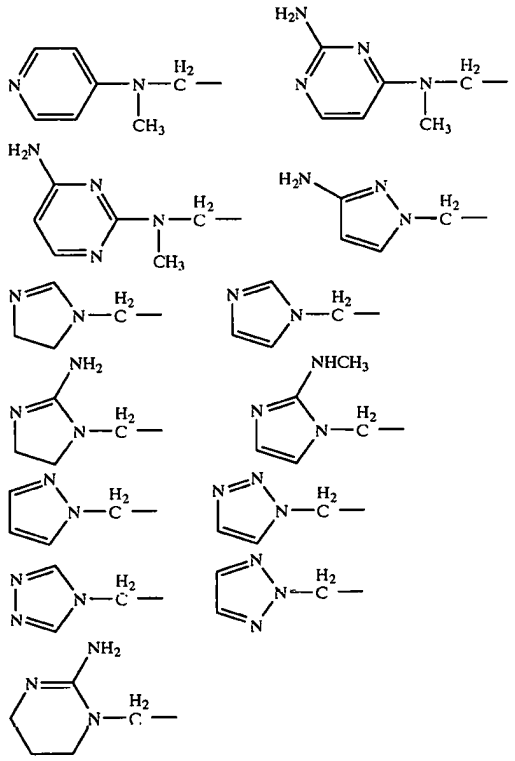


wherein:

R^{1a} is H or F;

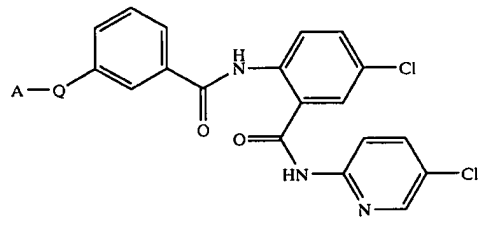
R^{1d1} is H or —OMe; and

A-Q is a member selected from the group consisting of:



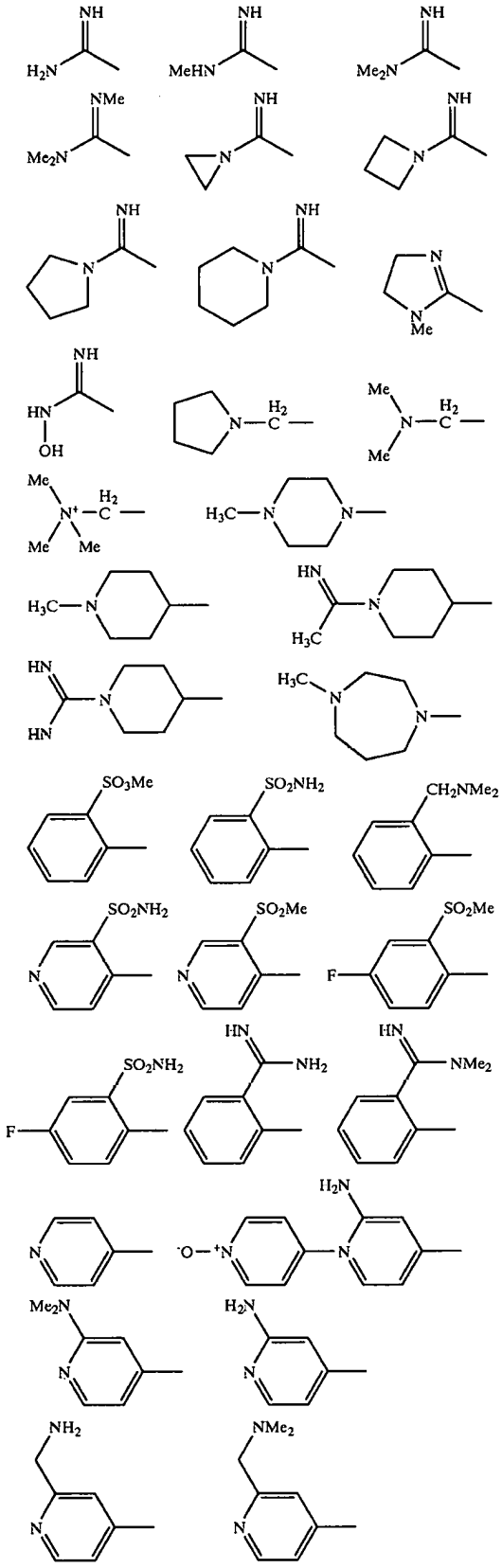
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



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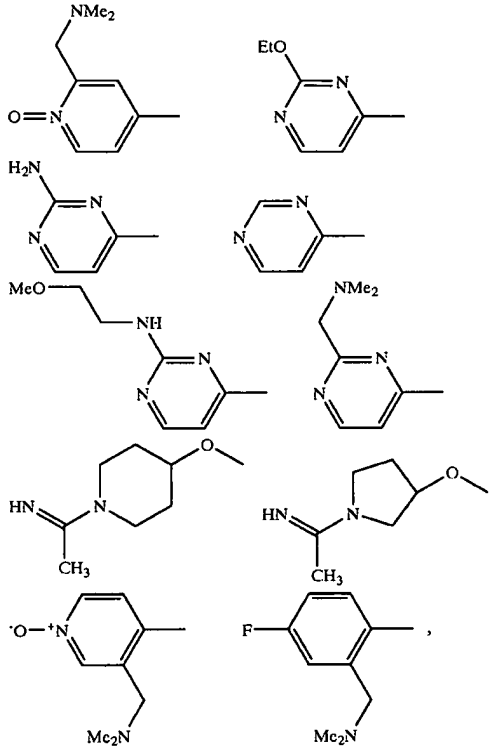
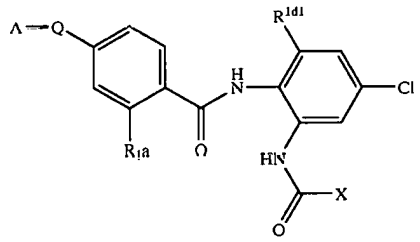


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

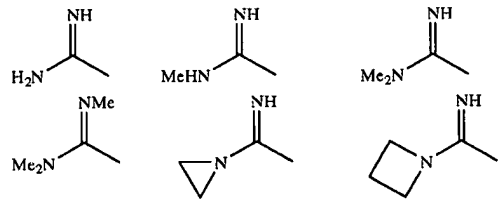


wherein:

R^{1a} is H or F;

R^{1d1} is H or —OMe;

A-Q is a member selected from the group consisting of:



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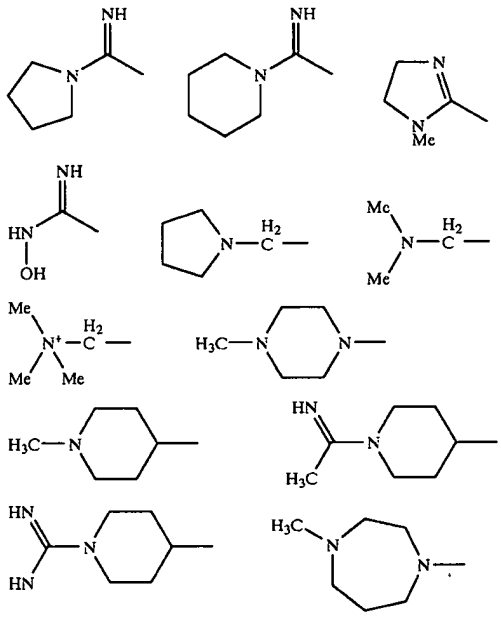

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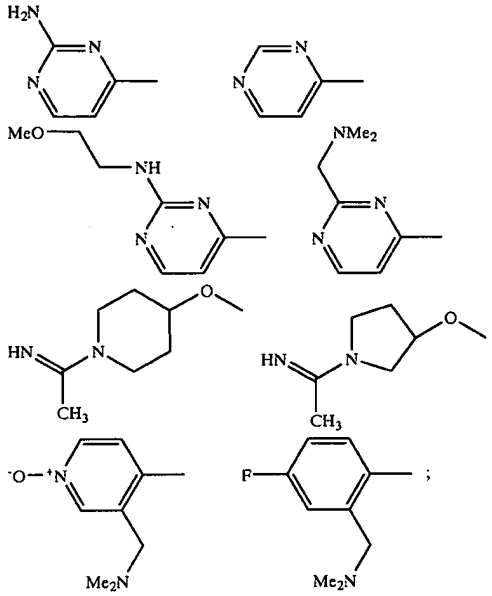
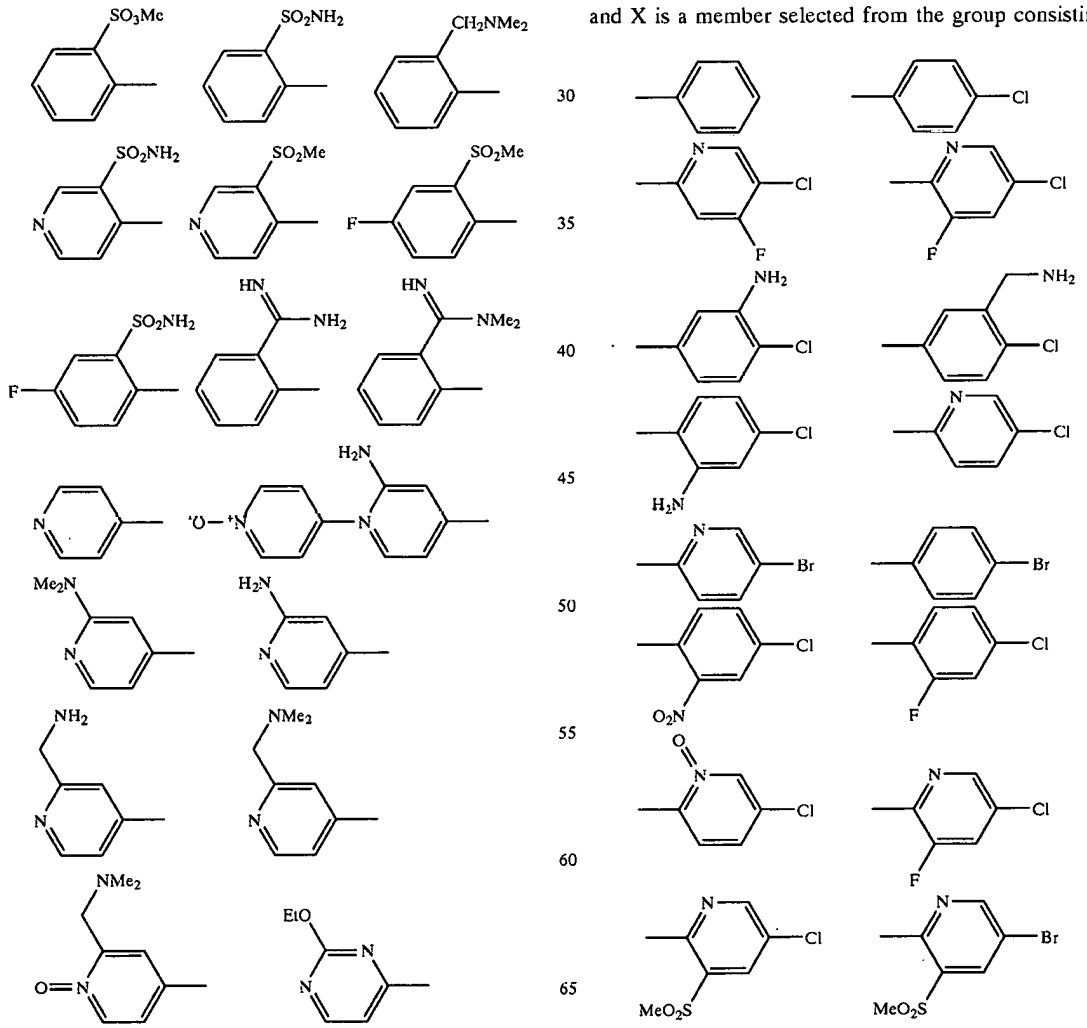


and X is a member selected from the group consisting of:



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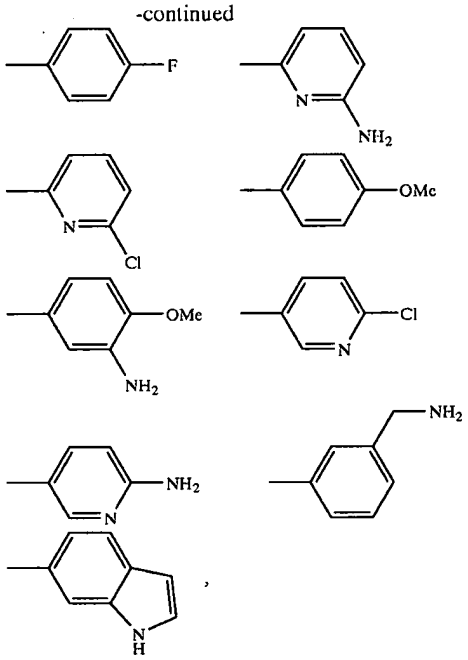
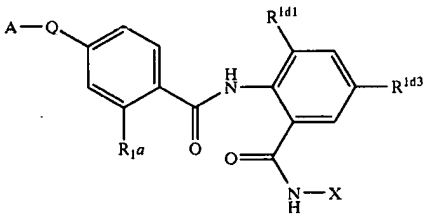


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

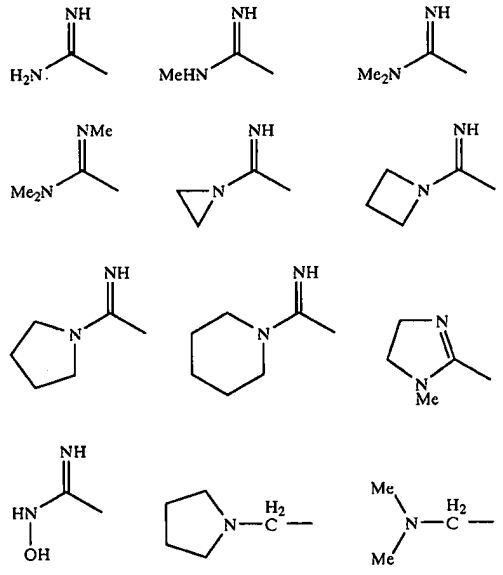
The invention provides compound of formula Ib, as describe above, having the following structure:



wherein:

R^{1a} is H or F;

A-Q is a member selected from the group consisting of:



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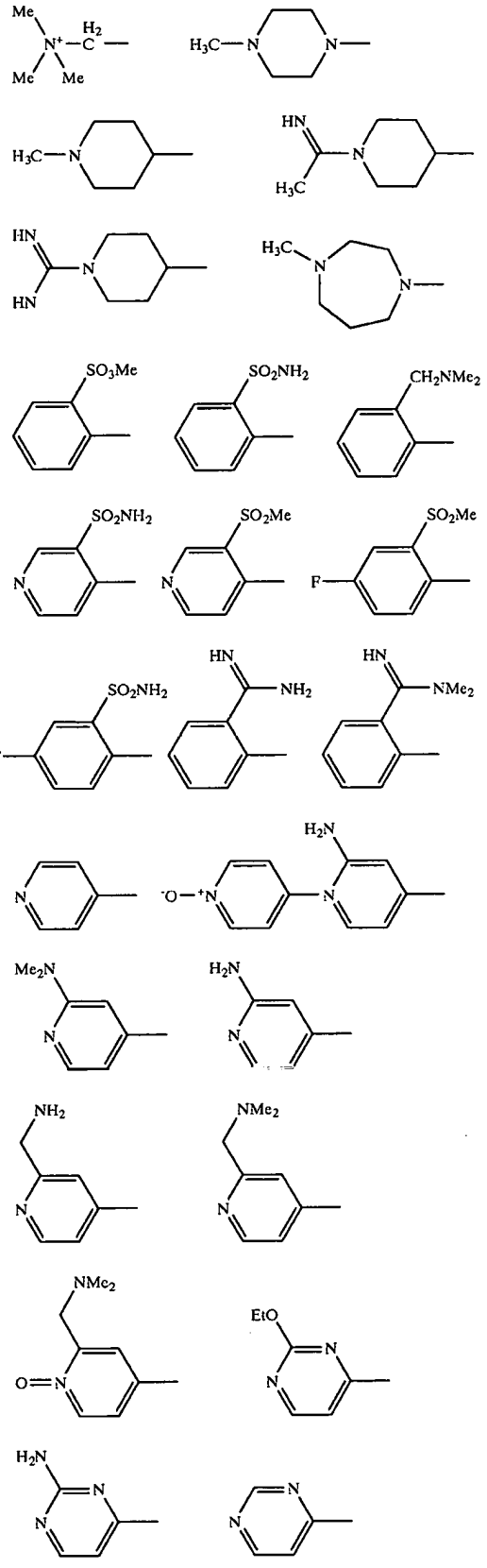

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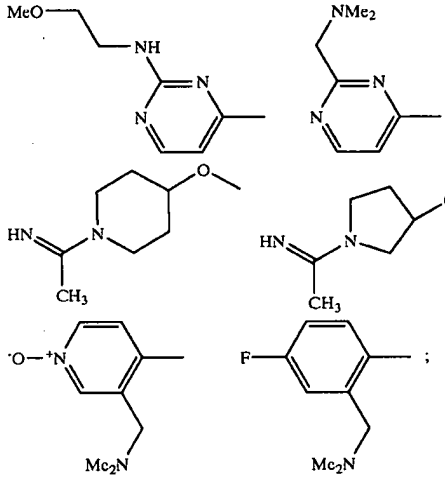
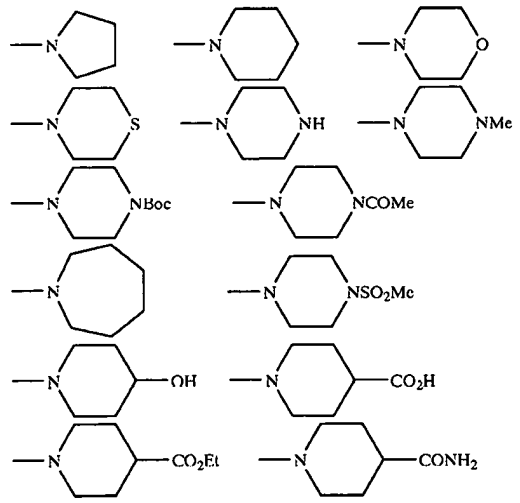
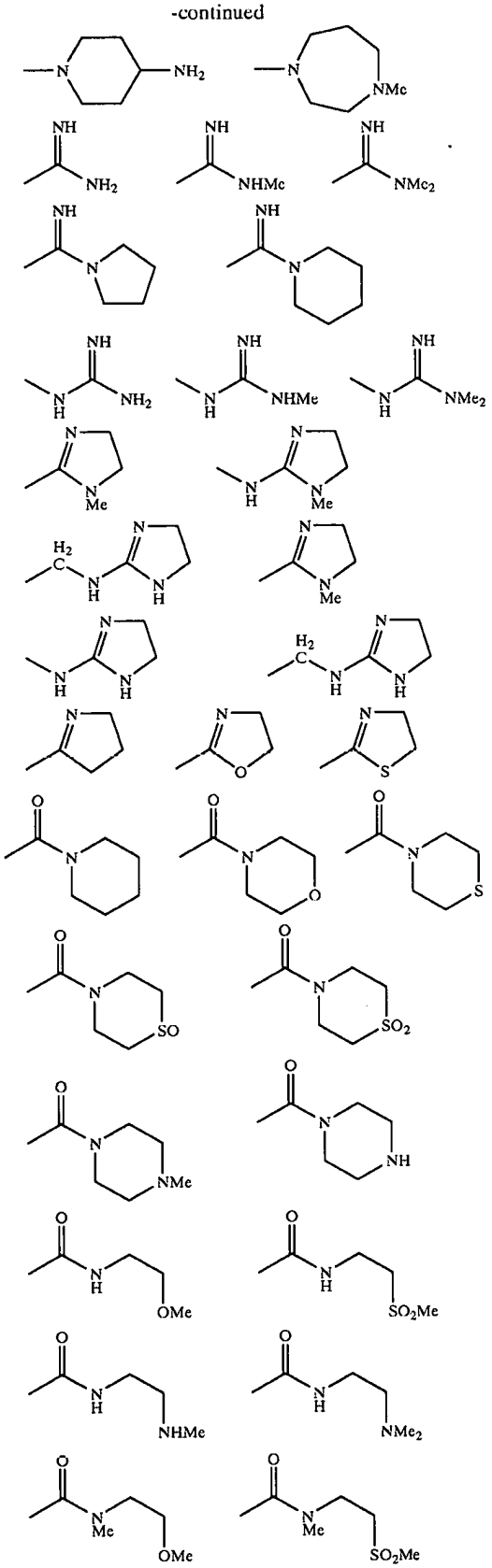


R^{1d1} is a member selected from the group consisting of:

H, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,





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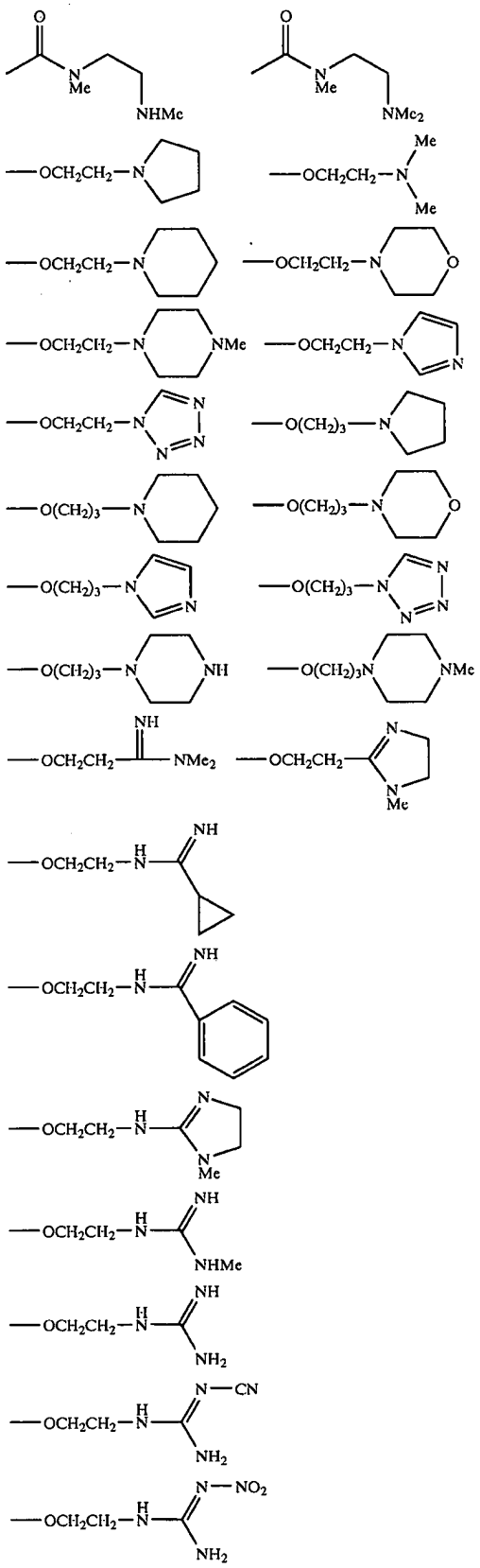

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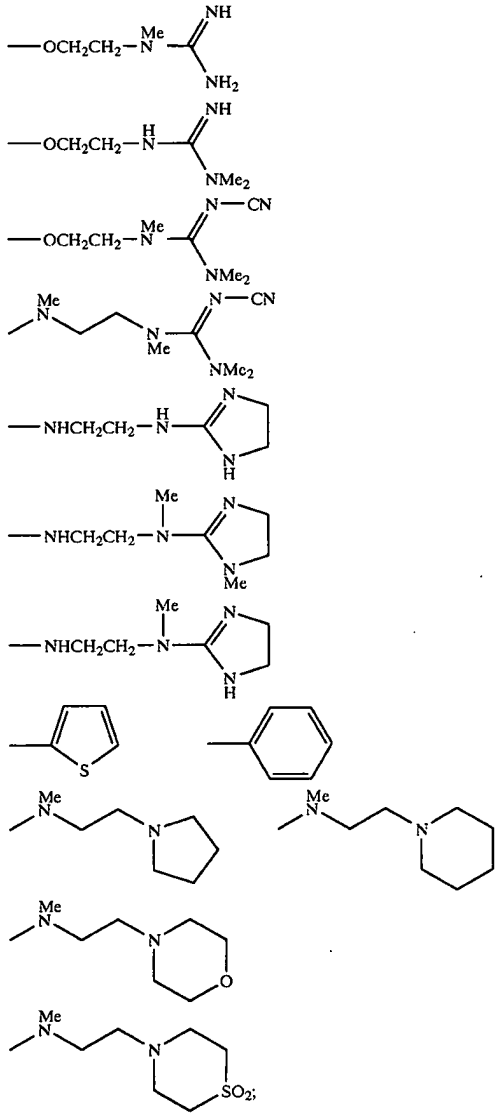
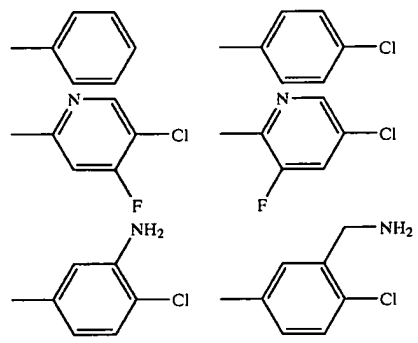


R^{1d3} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3; and

X is a member selected from the group consisting of:



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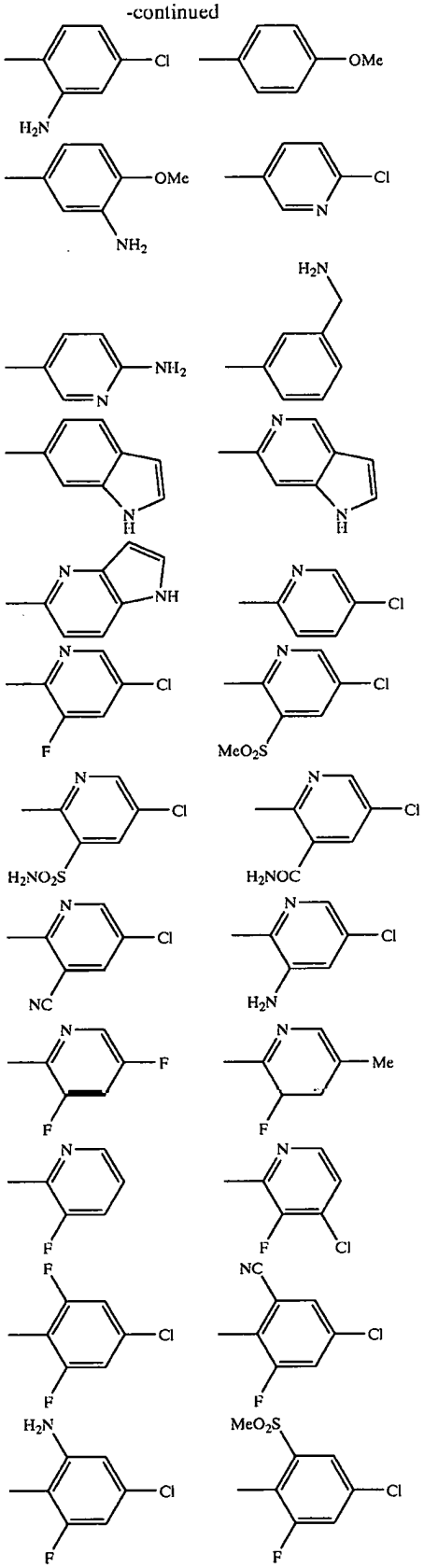

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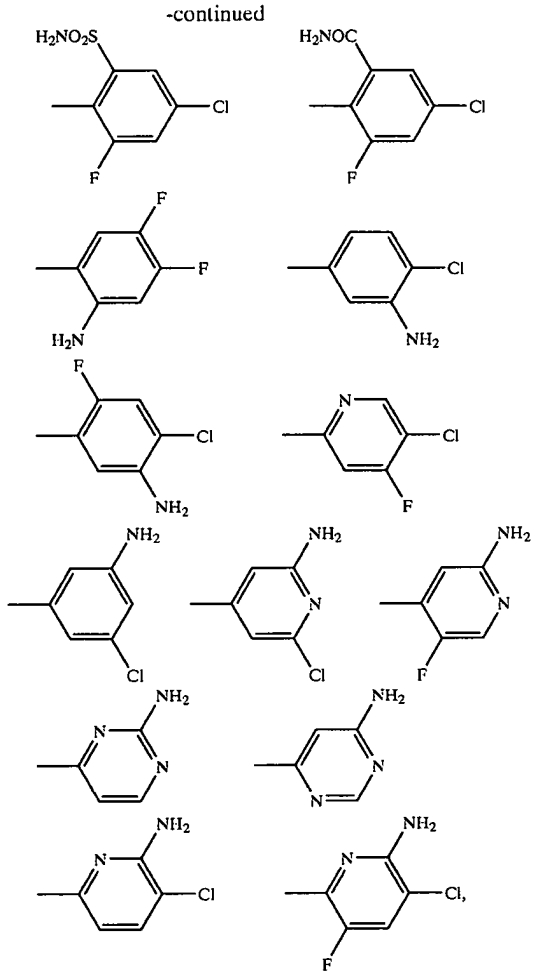
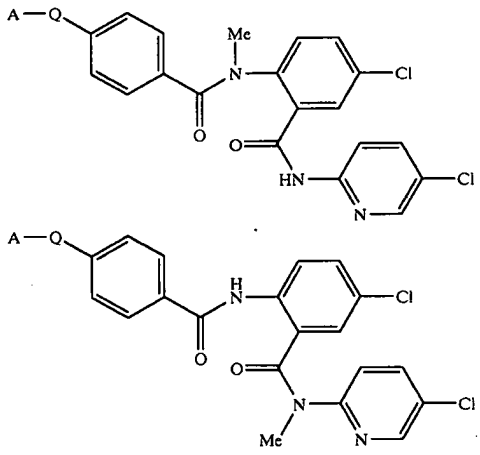


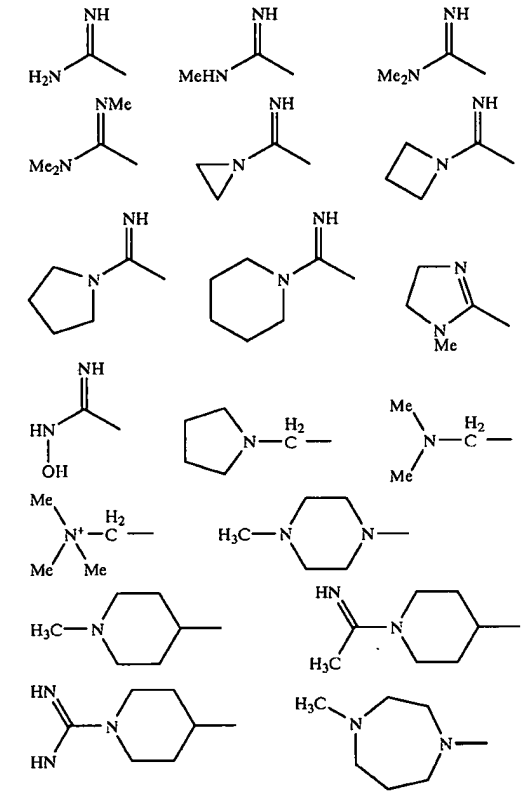
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

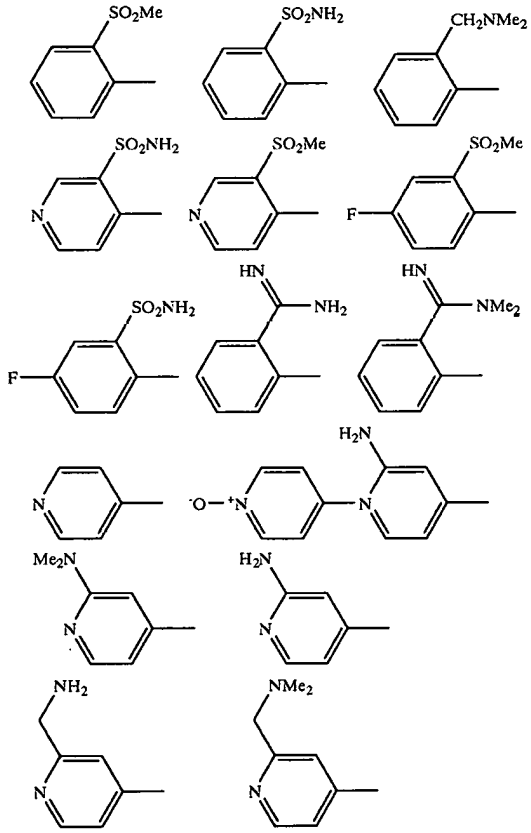
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:





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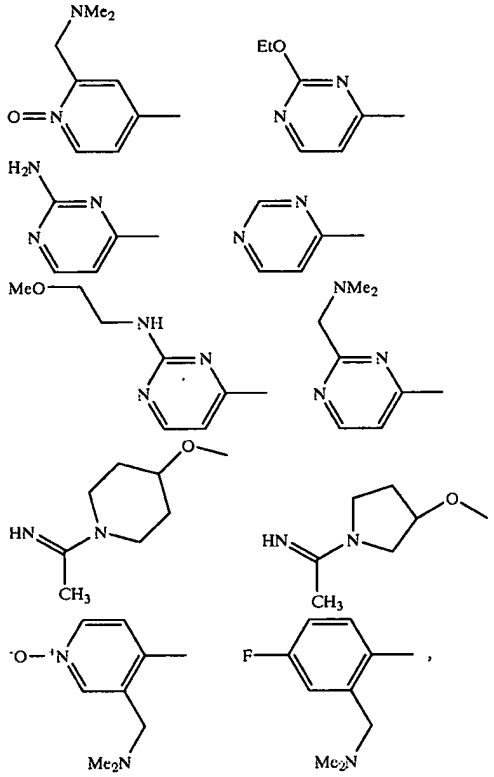
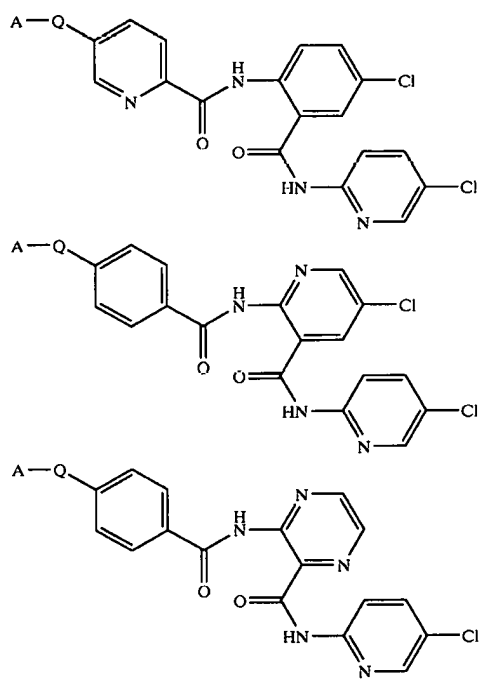


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



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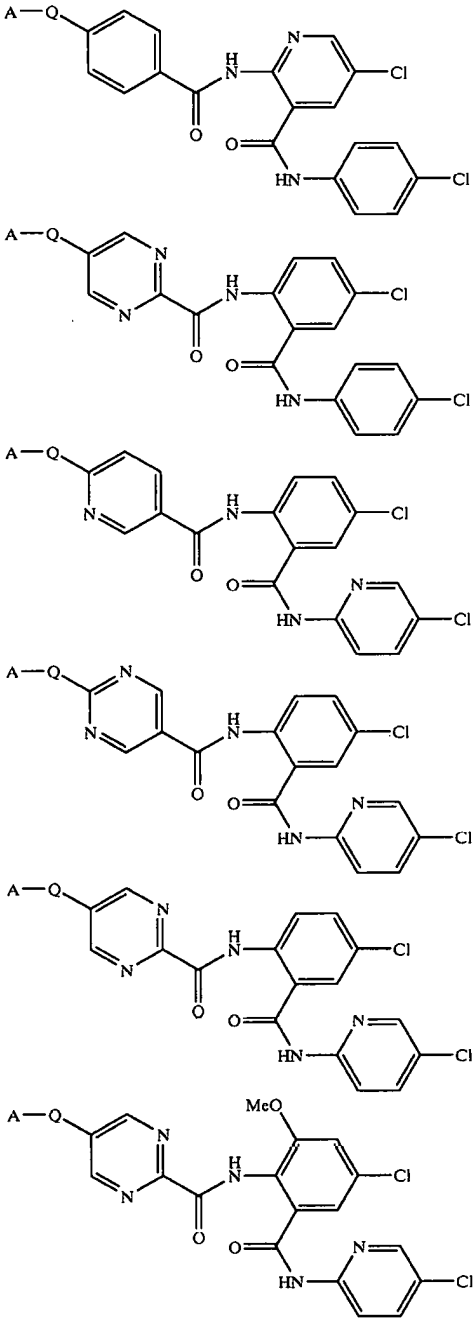

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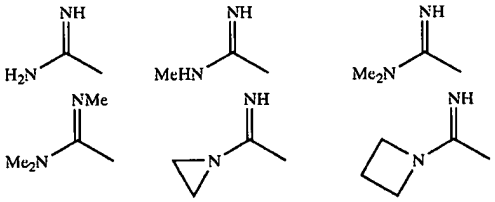
A-Q is a member selected from the group consisting of:



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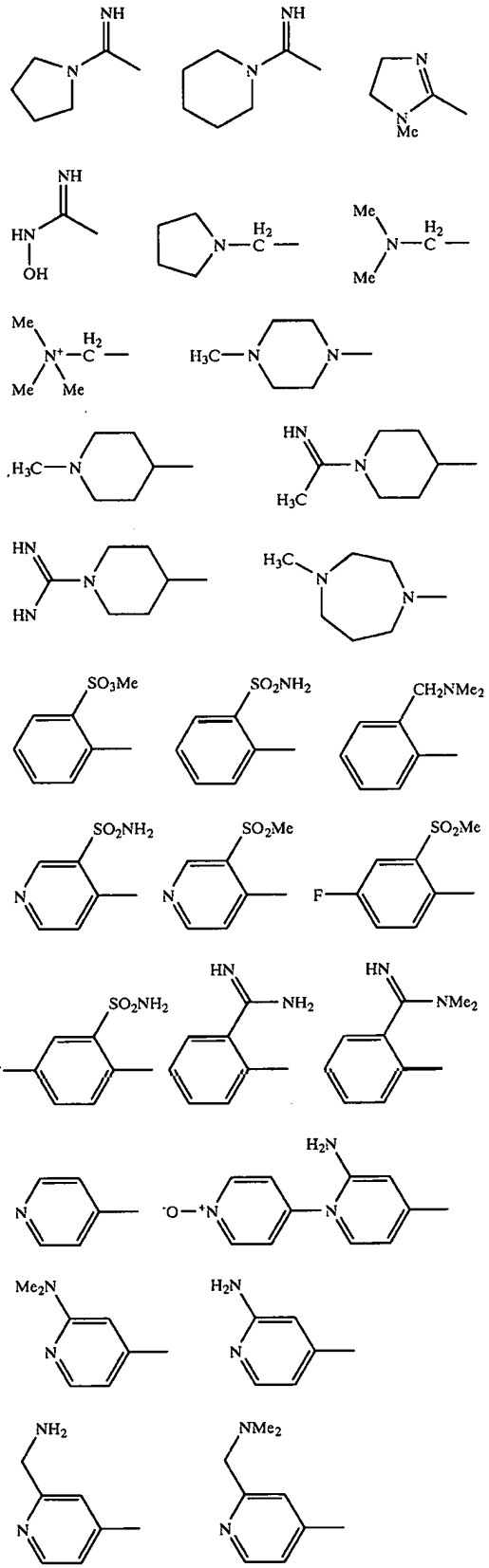

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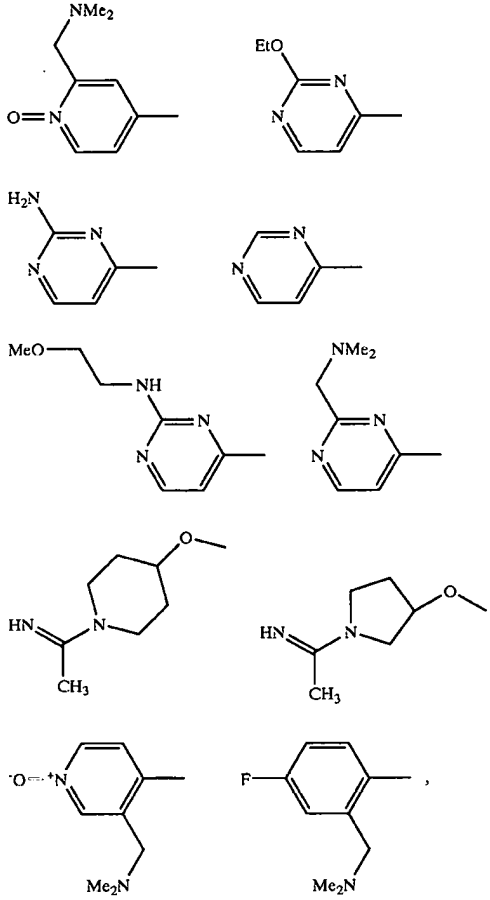

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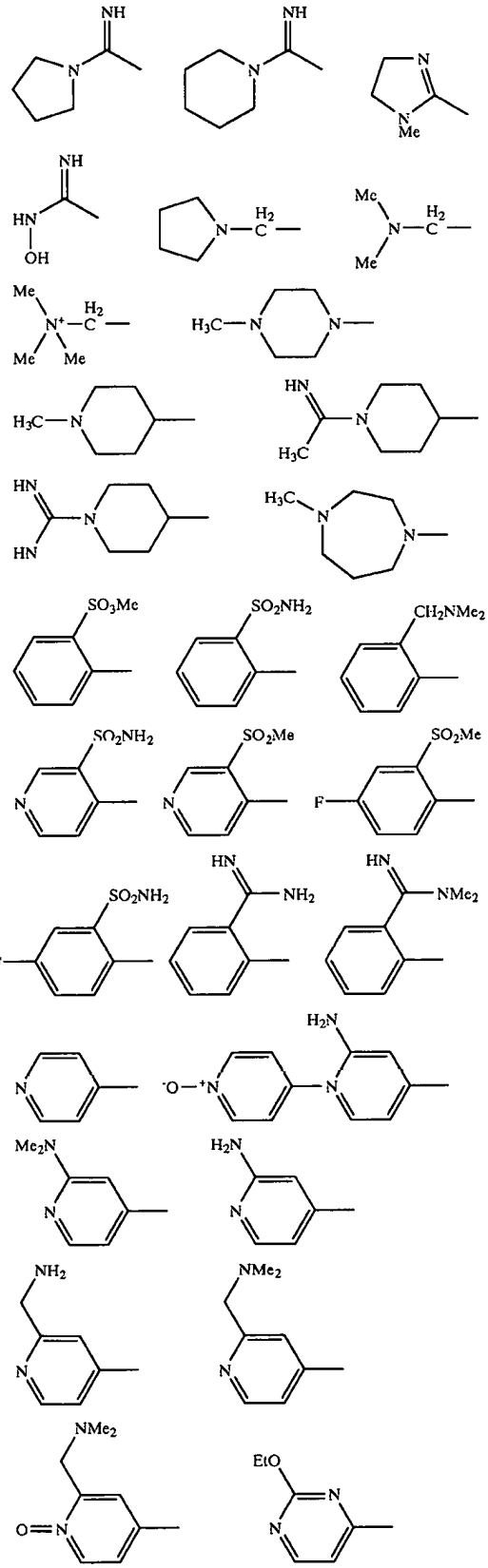
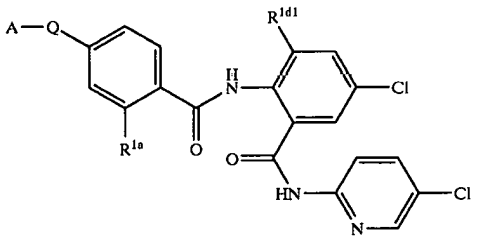


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof:

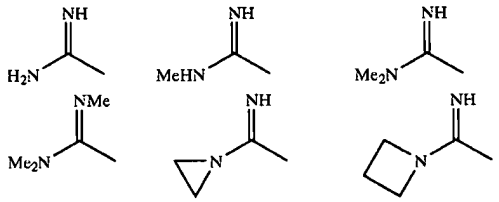
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is H or F;

A-Q is a member selected from the group consisting of:



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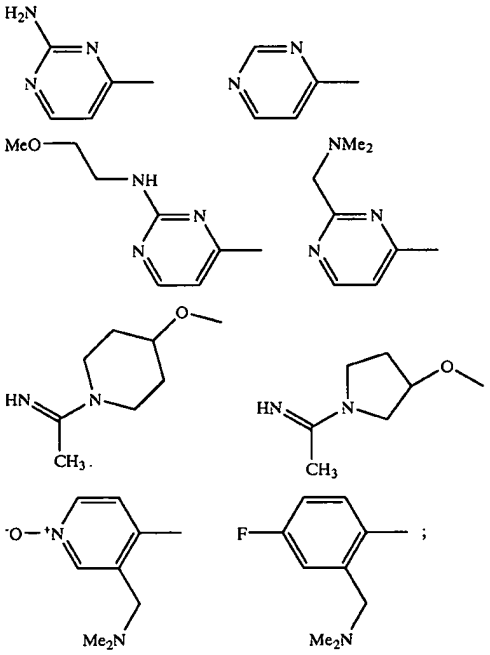

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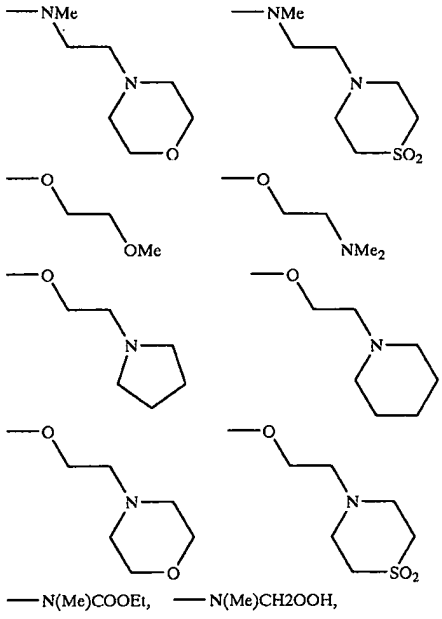
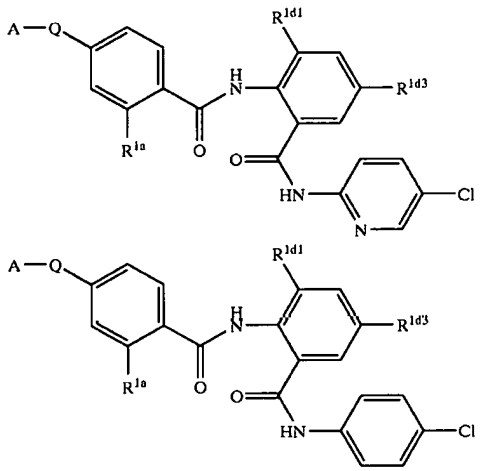


—N(Me)COOEt, —N(Me)CH2OOH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

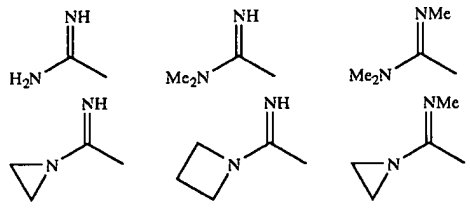
The invention provides compound of formula Ib, as described above, having the following structure:



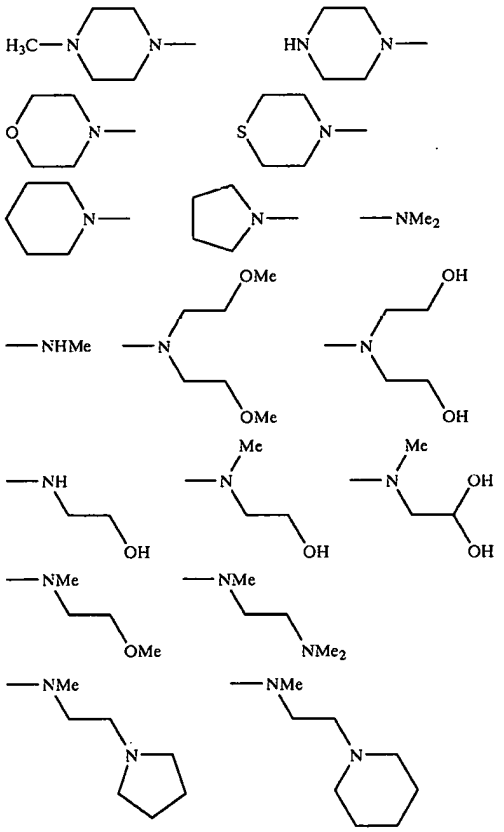
wherein:

R^{1a} is H or F;

A-Q is a member selected from the group consisting of:



R^{1d1} is a member selected from the group consisting of: H, OMe, Cl, F, OCF_3,



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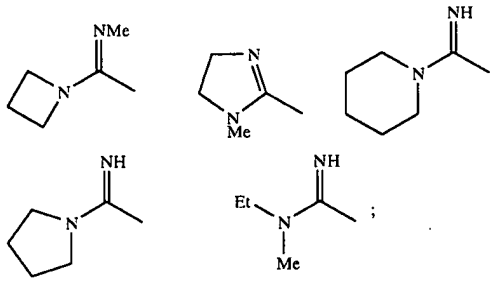
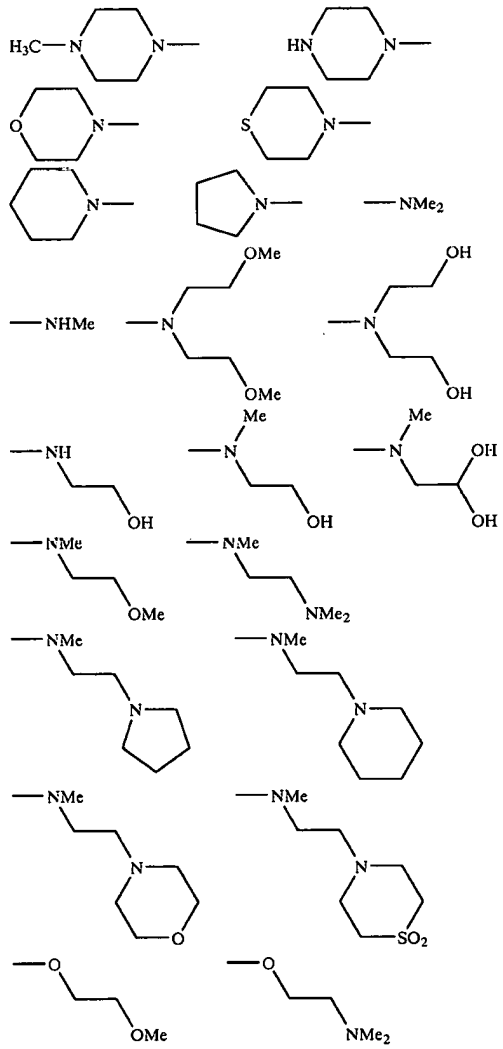


R^{1d1} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OCF_3, —OH, —NMe_2, —OCH_2CO_2Et, —OCH_2CO_2H;

R^{1d3} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OCF_3, —OH, —NMe_2, —OCH_2CO_2Et, —OCH_2CO_2H, —OCF_2H, —$OCFH_2$, —OCF_2CF_3, —OCH_2CH_3,



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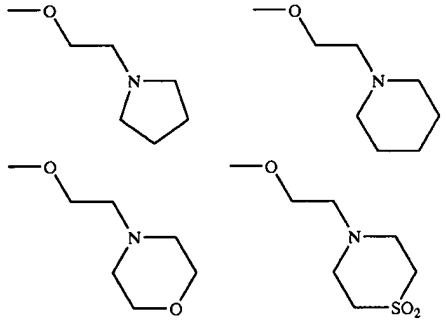
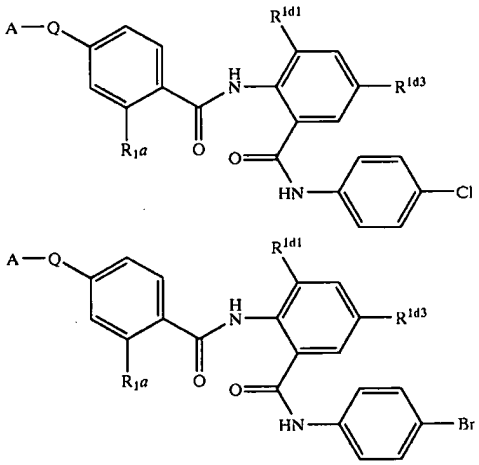


—N(Me)COOEt, —N(Me)CH_2OOH

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

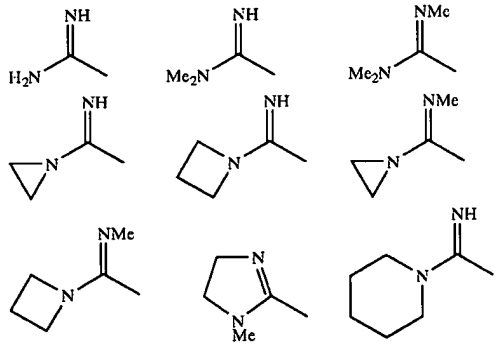
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R1a is H or F;

A-Q is a member selected from the group consisting of:



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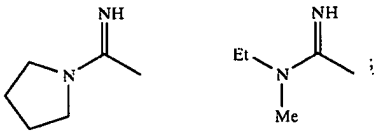

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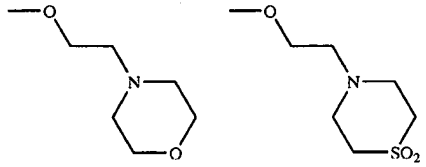
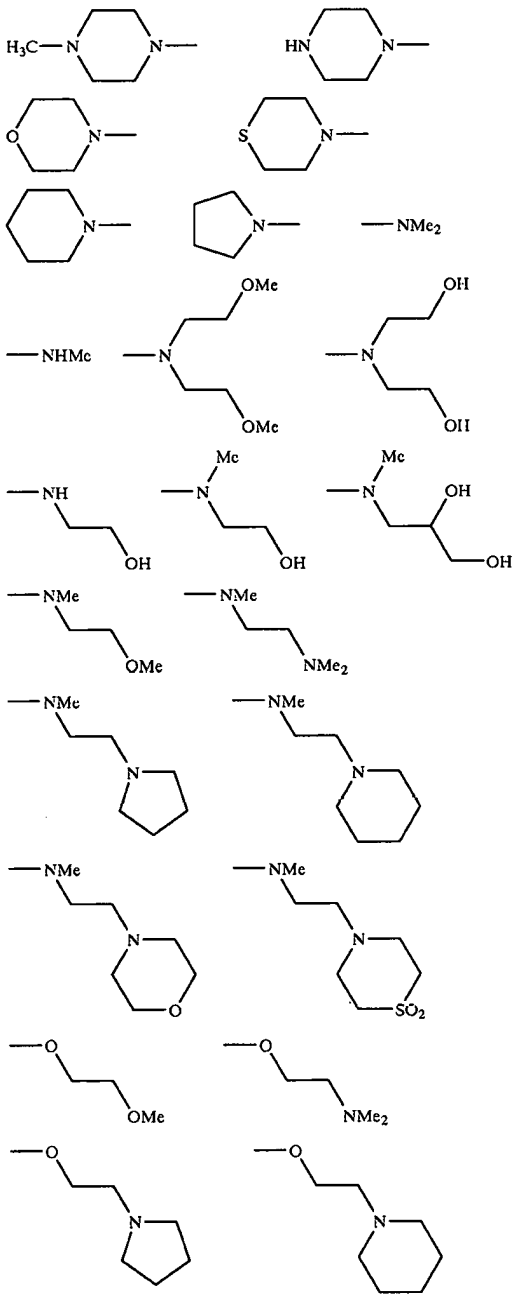


R^{1d1} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OCF_3, —OH, —NMe_2, —OCH_2CO_2Et, —OCH_2CO_2H



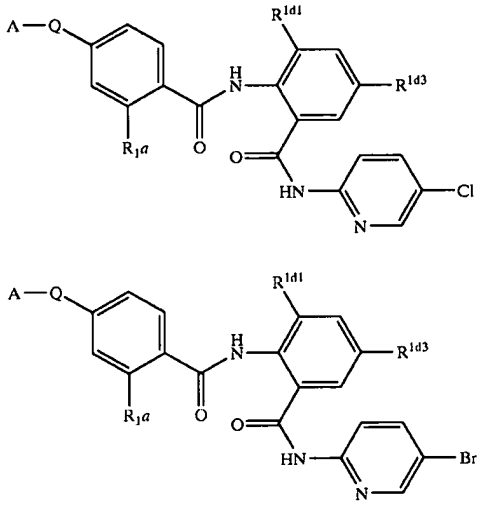
—N(Me)COOEt, —$N(Me)CH_2OOH$

R^{1d3} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OCF_3, —OH, —NMe_2, —OCH_2CO_2Et, —OCH_2CO_2H, —OCF_2H, —$OCFH_2$, —OCF_2CF_3, —OCH_2CH_3.

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

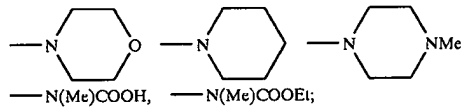
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is H or F;

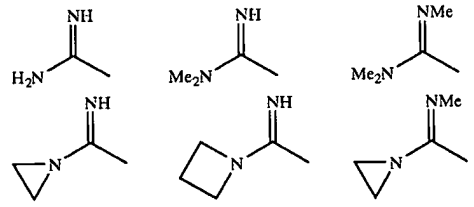
R^{1d1} is selected from H, —OMe, —NMe_2,



—N(Me)COOH, —N(Me)COOEt;

R^{1d3} is Cl or Br;

A-Q is a member selected from the group consisting of:



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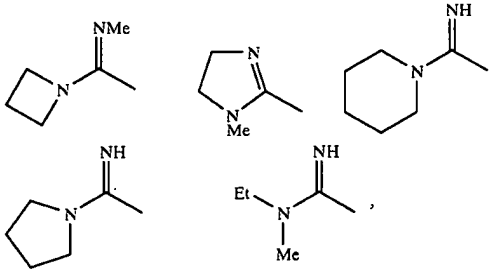
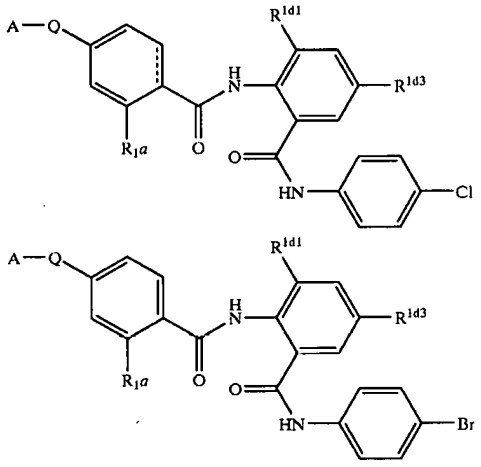


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

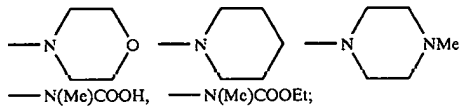
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

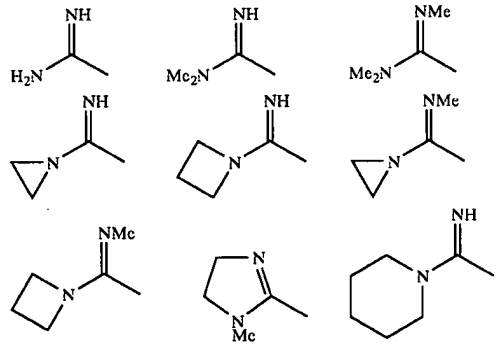
R^{1a} is H or F;

R^{1d1} is selected from H, —OMe, —NMe_2,



R^{1d3} is Cl or Br;

A-Q is a member selected from the group consisting of:



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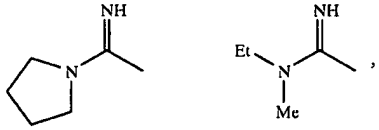
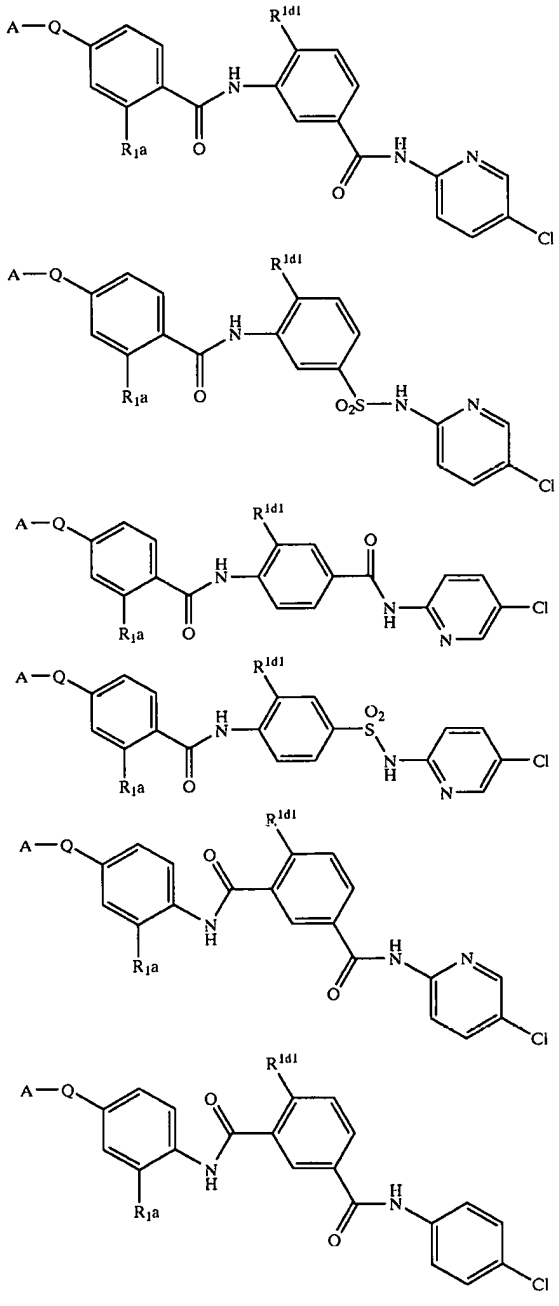


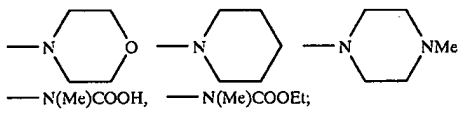
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

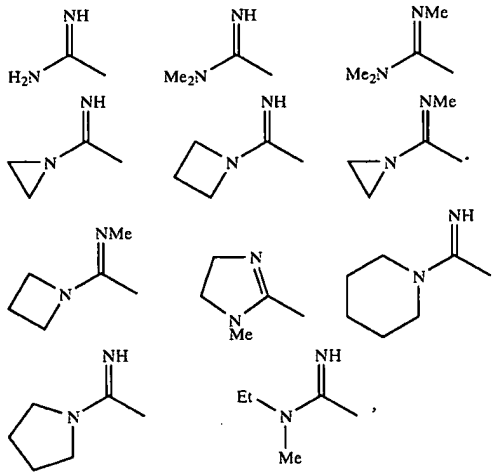


wherein:

R^{1a} is H or F;
R^{1d1} is selected from H, —OMe, —NMe_2,

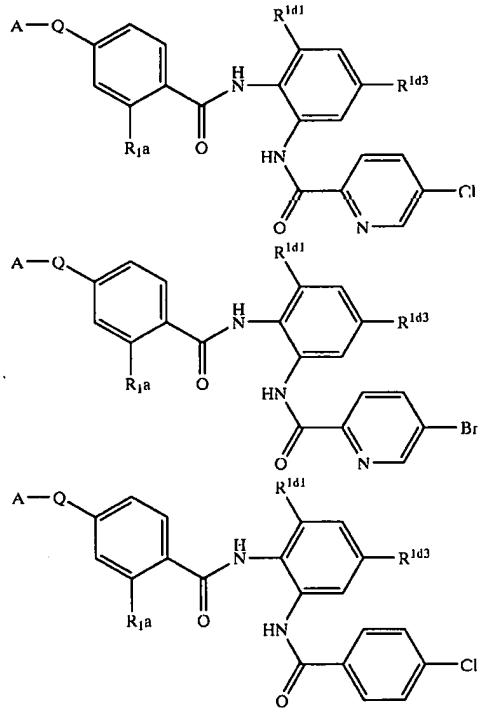


A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



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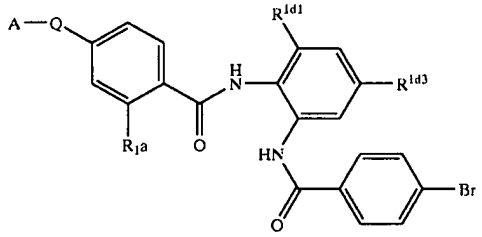
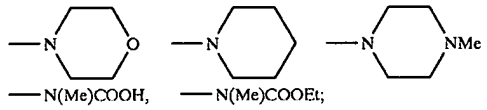
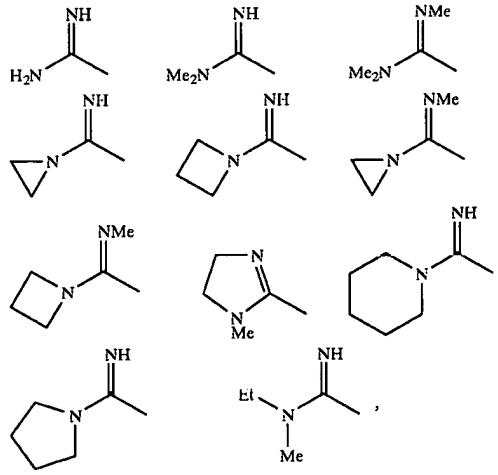


wherein:

R^{1a} is H or F;
R^{1d1} is selected from H, —OMe, —NMe_2,

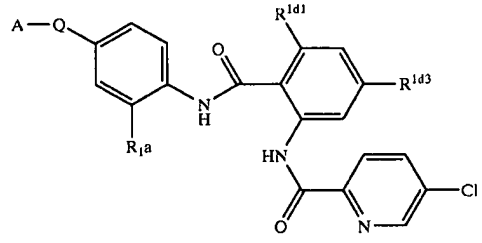


R^{1d3} is —Cl or —Br,
A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides a compound of formula Ib, as described above, having the following structure:



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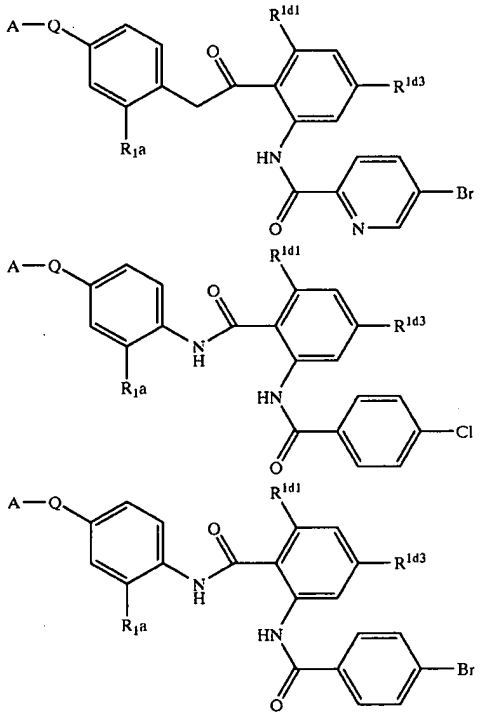
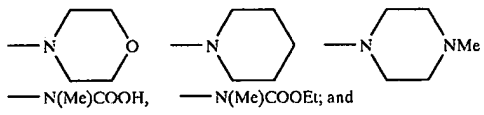


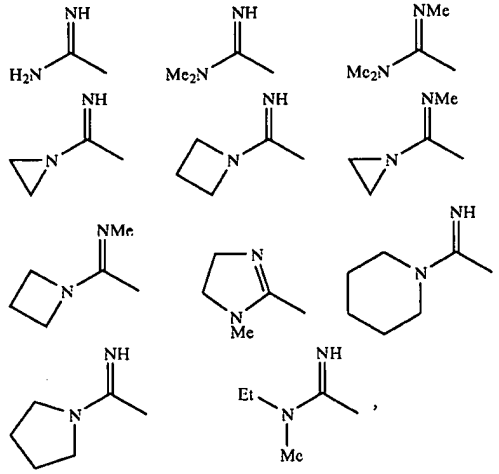
wherein:

R^{1a} is H or F;
R^{1d1} is selected from H, —OMe, —NMe_2,



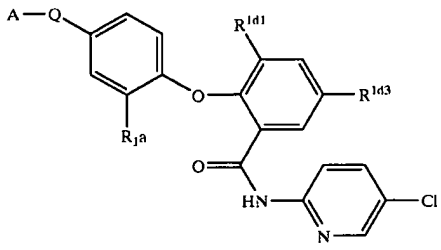
—N(Me)COOH, —N(Me)COOEt; and

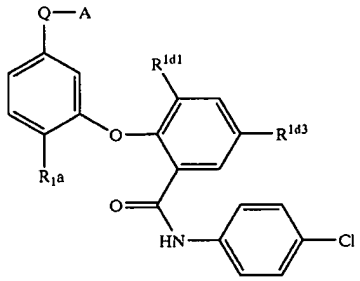
R^{1d3} is —Cl or —Br,
A-Q is a member selected from the group consisting of:

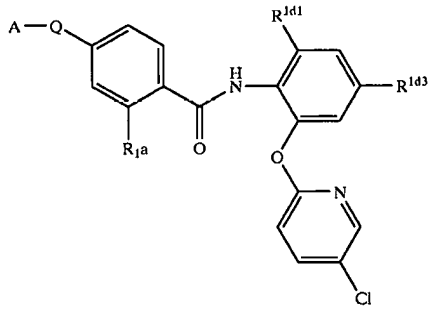


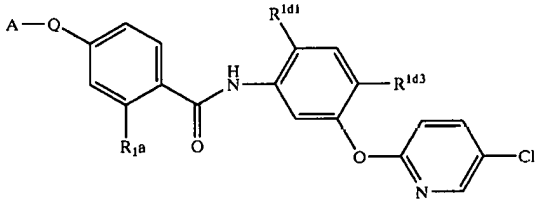
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



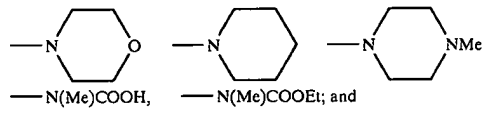






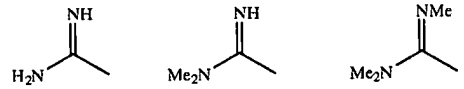
wherein:

R^{1a} is H or F;
R^{1d1} is selected from H, —OMe, —NMe_2,



—N(Me)COOH, —N(Me)COOEt; and

A-Q is a member selected from the group consisting of:



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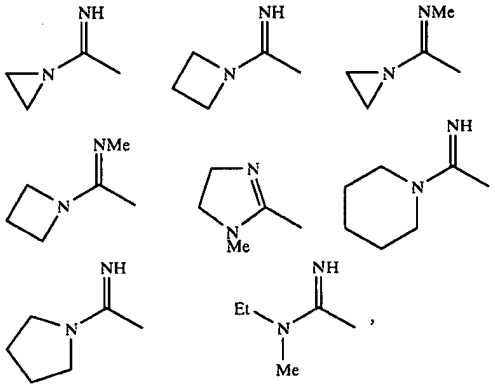
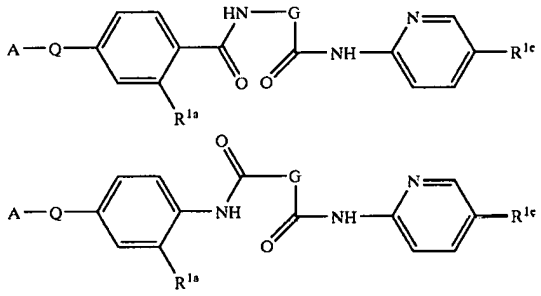


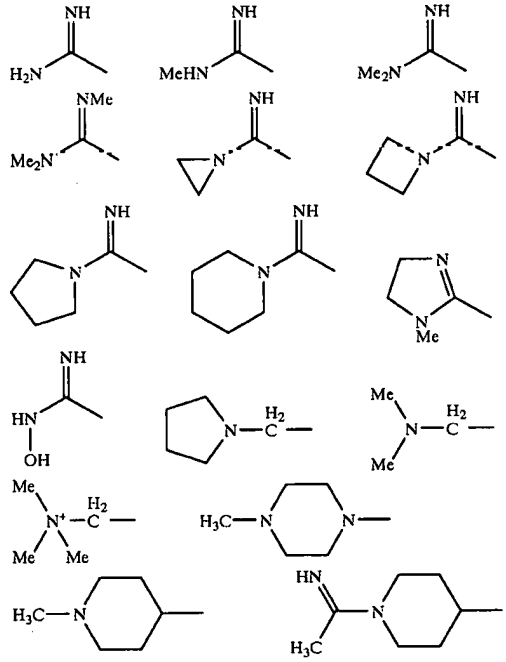
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



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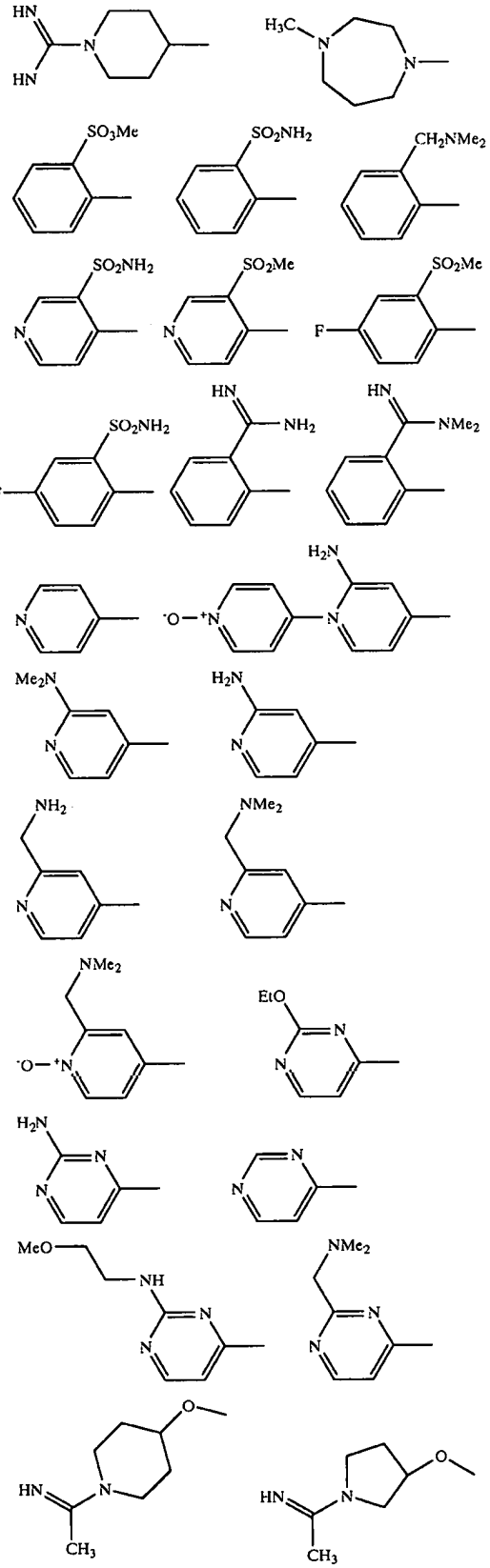

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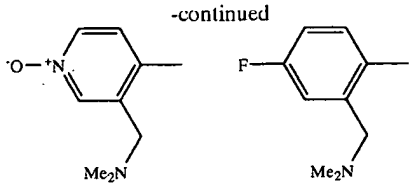


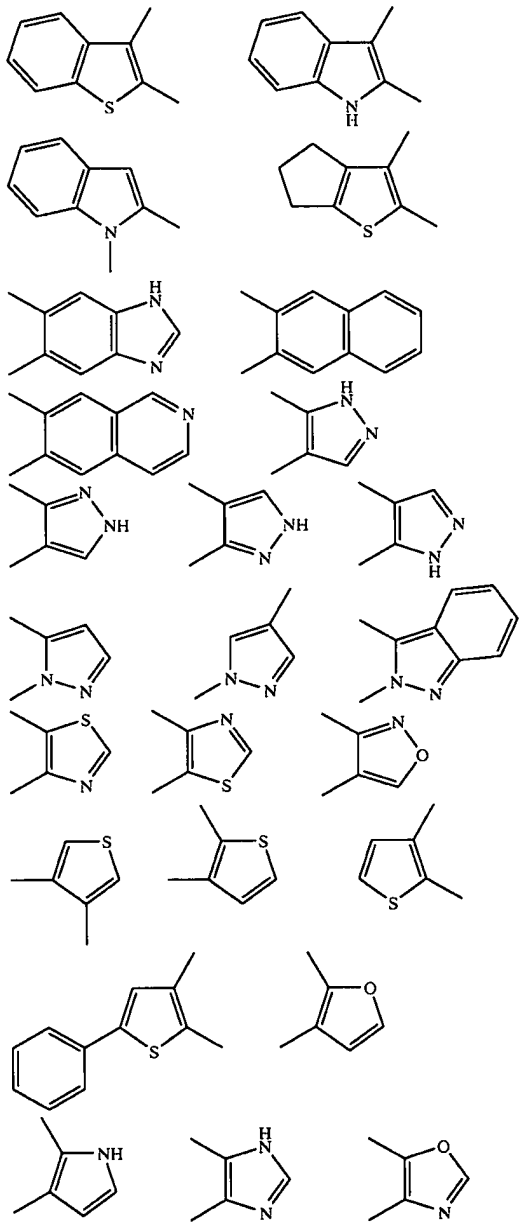
R^{1a} is a member selected from the group consisting of:

H, —F, —Cl and Br;

R^{1e} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2; and

G is a member selected from the group consisting of:



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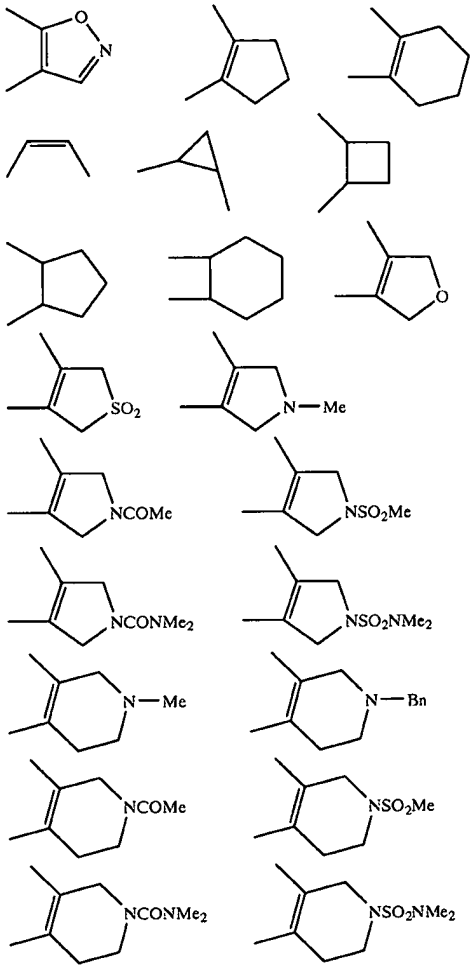

wherein each G group is substituted by 0–4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —NHCH2CONHMe, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,

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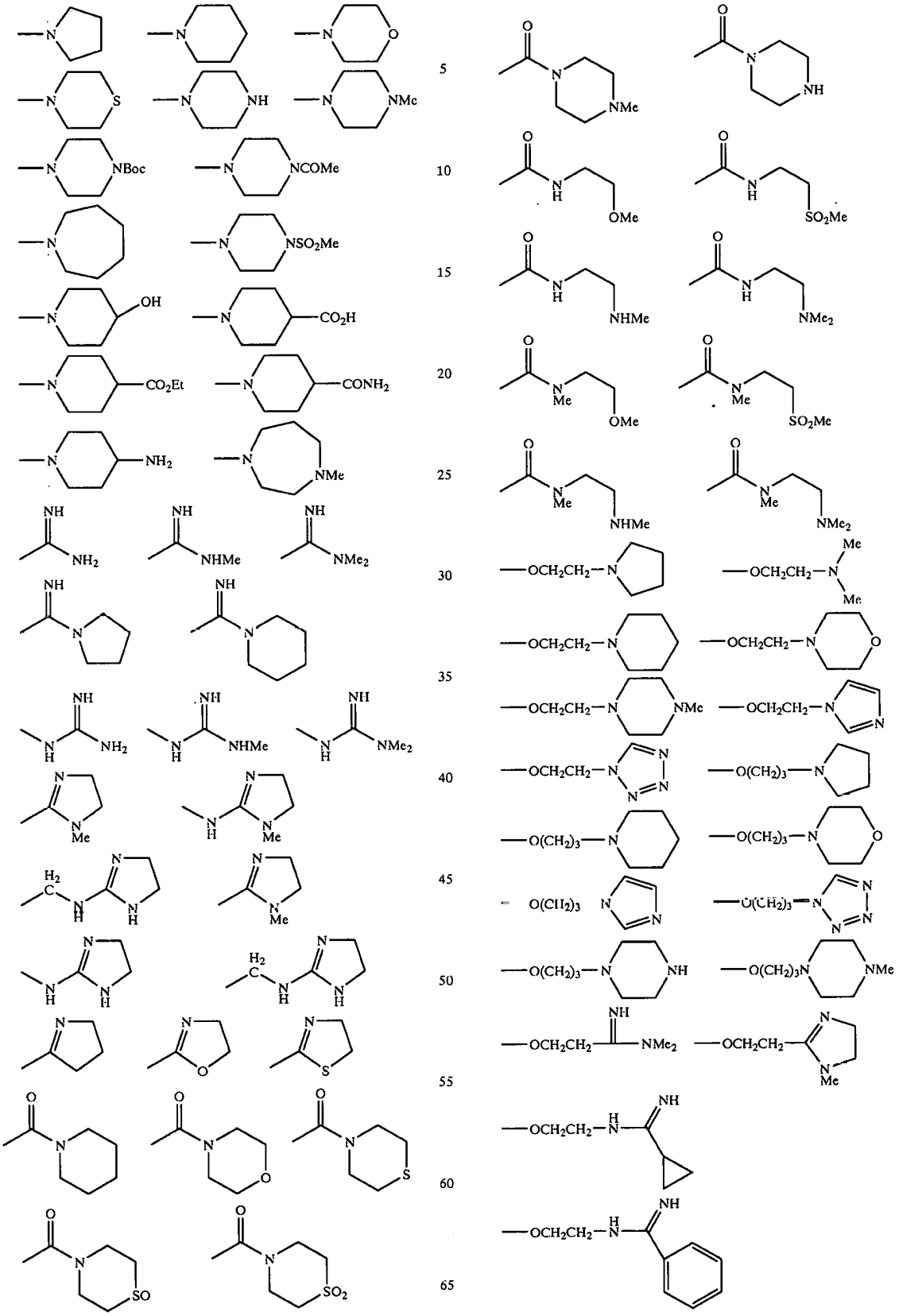

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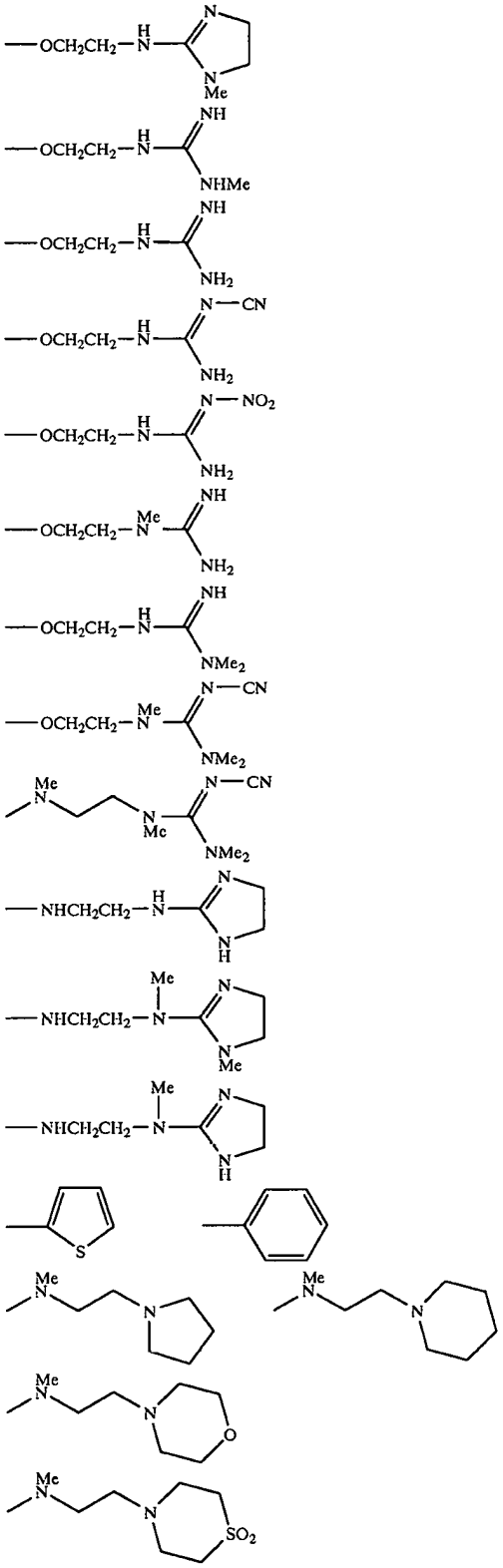
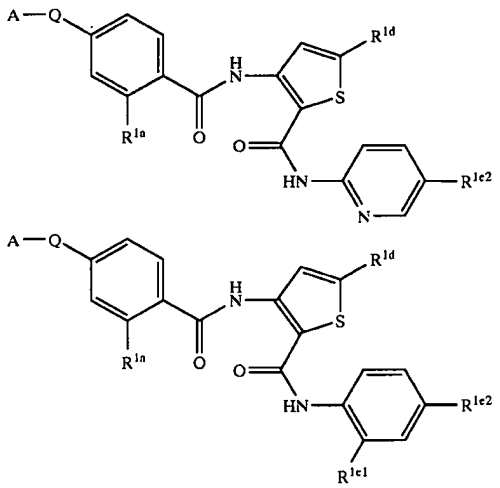


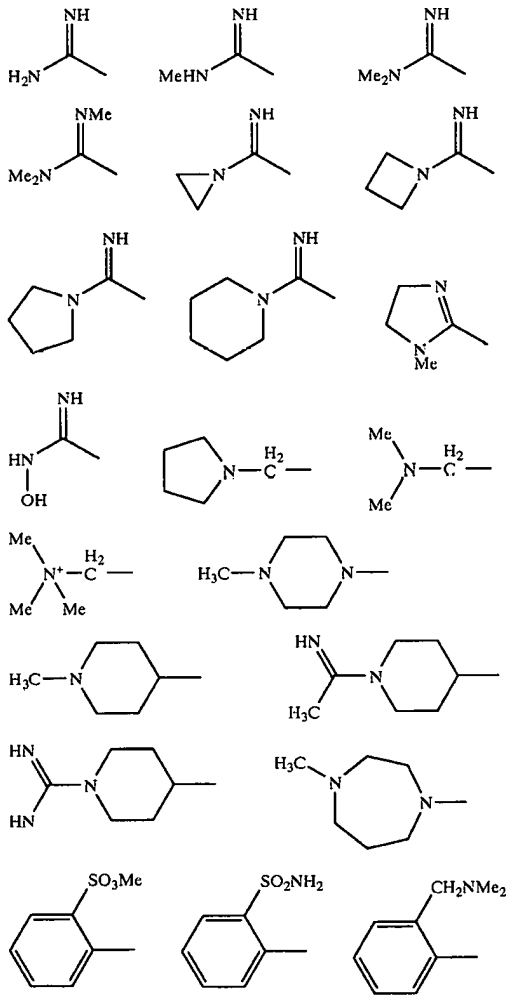
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group of:



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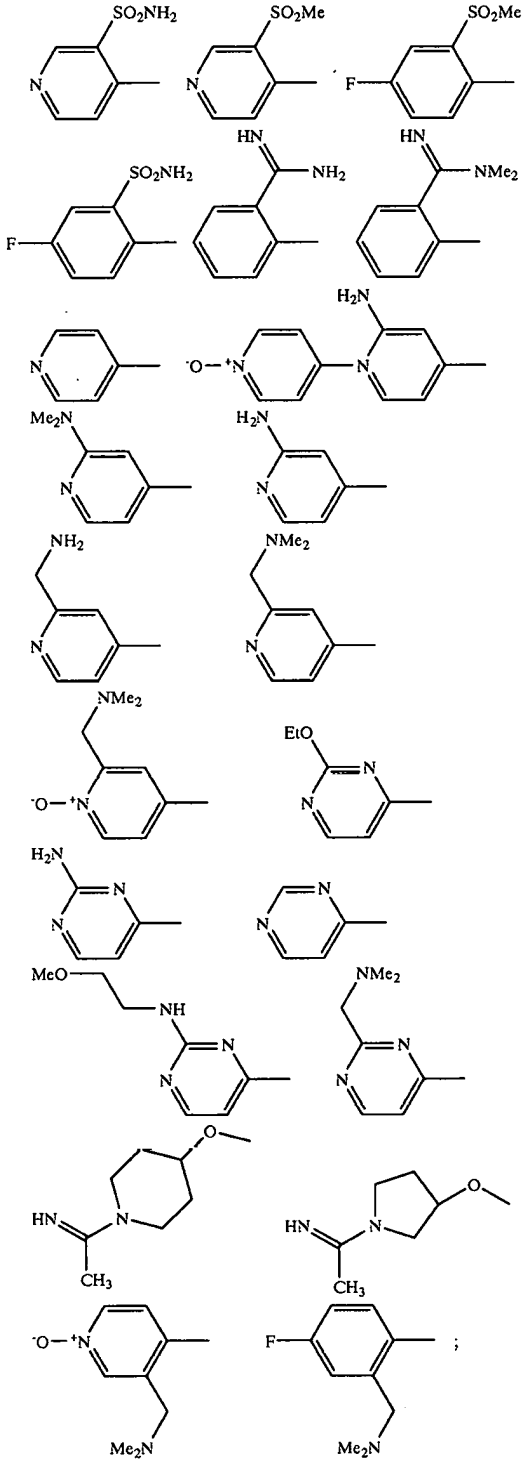


R^{1a} is a member selected from the group of:

H, —F, —Cl, —Br;

R^{1d} is a member selected from the group of:

H, —F, —Cl, —Br, —OMe;

R^{1e1} is a member selected from the group of:

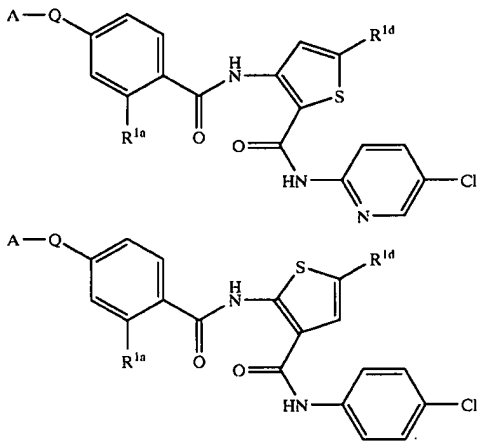
H, —F, —Cl, —Br, $—NH_2$, $—CH_2NH_2$, —OMe, —OH, —CN, $—SO_2Me$, $—SO_2NH_2$; and

R^{1e2} is a member selected from the group of:

H, —F, —Cl, —Br, $—NH_2$,

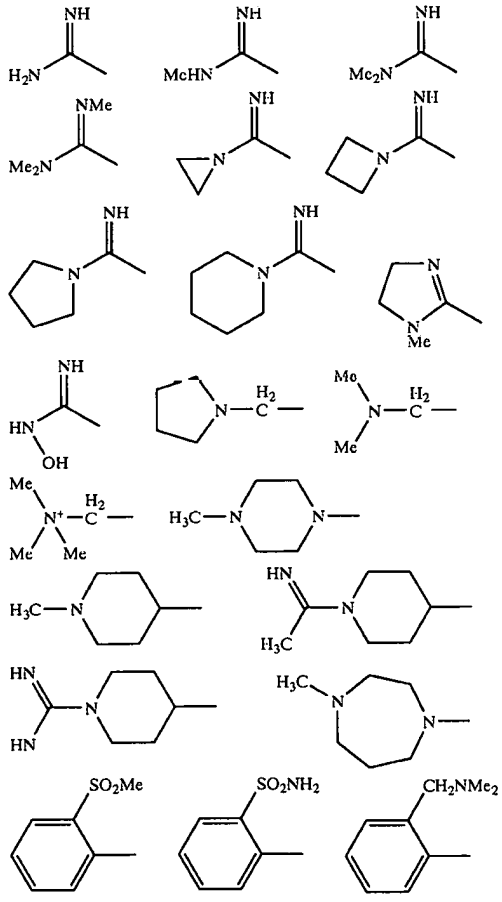
and all pharmaceutically acceptable isomers. salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group of:



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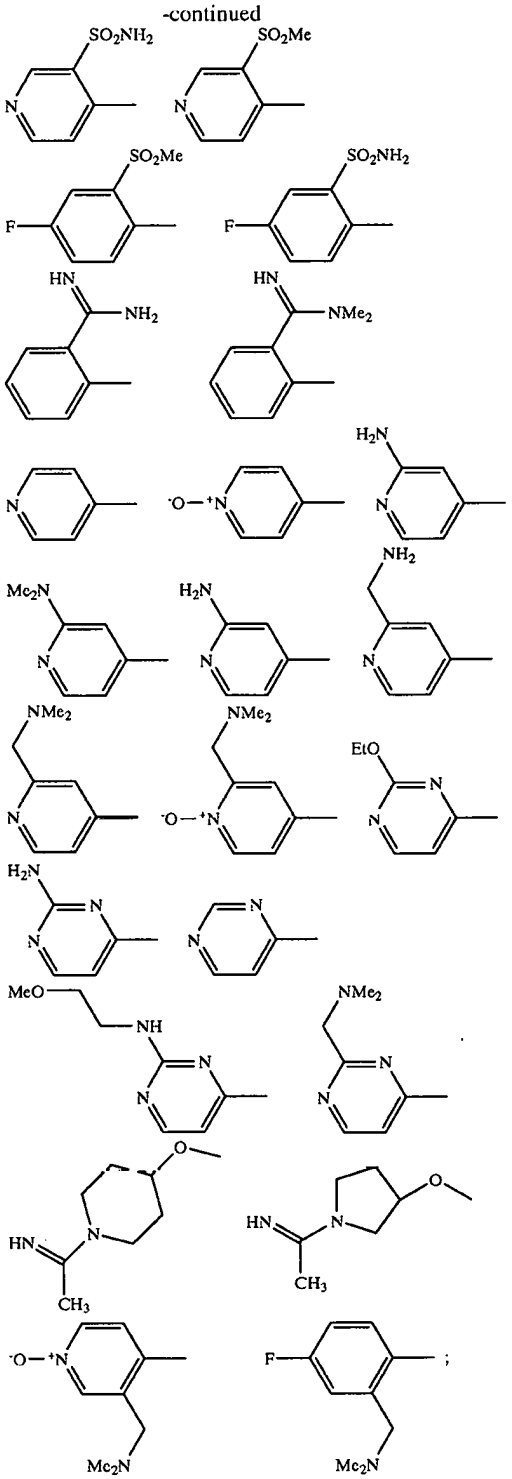
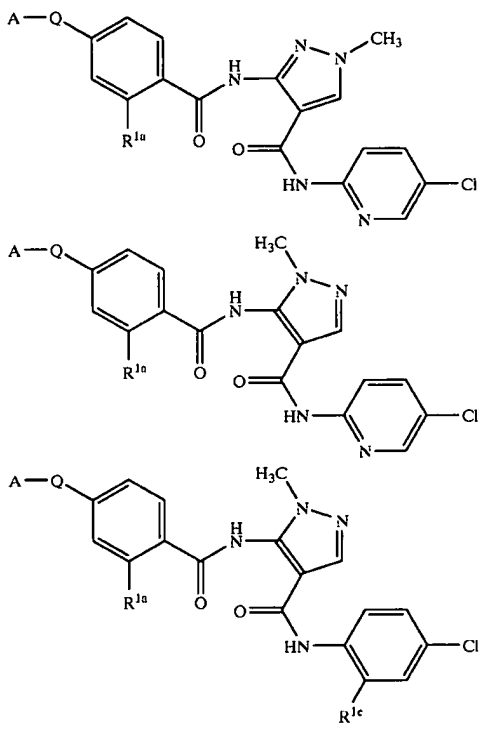


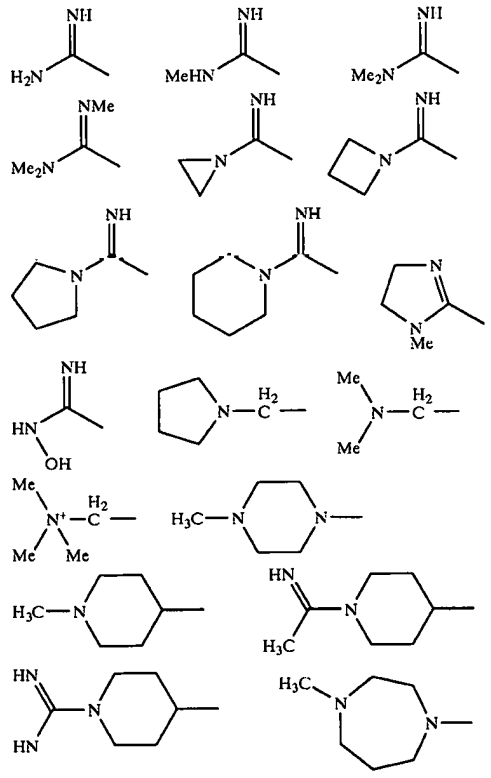
R^{1a} is a member selected from the group of:
H, —F, —Cl and Br; and
R^{1d} is a member selected from the group of:
H, —F, —Cl, —Br, —OMe,
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group of:



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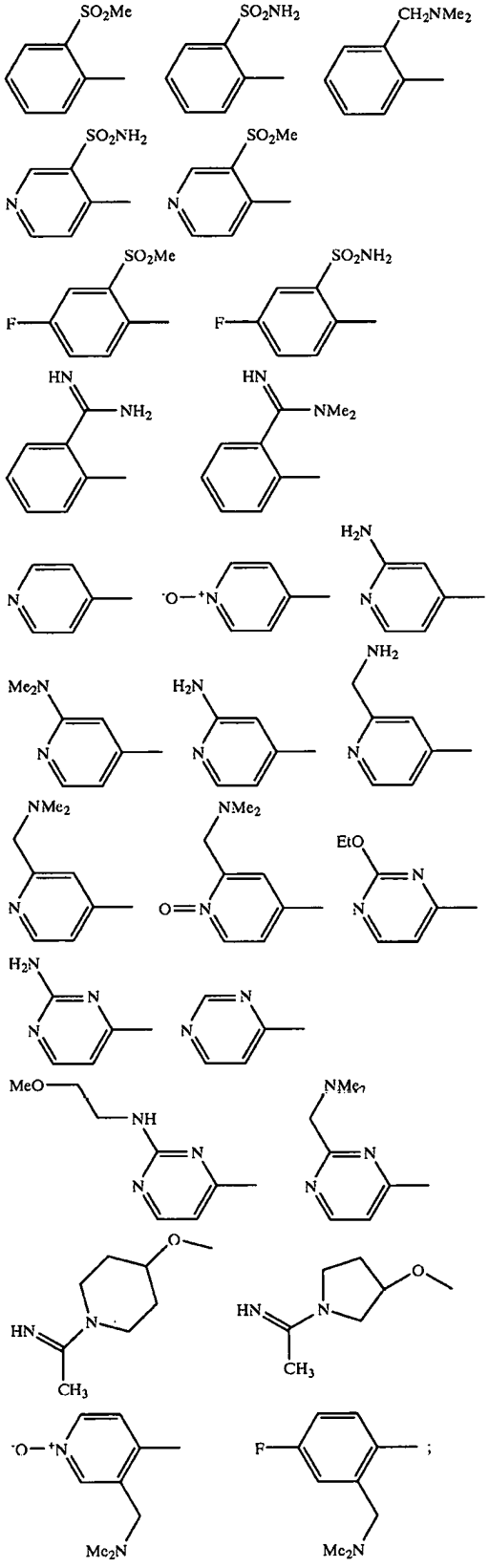


R^{1a} is a member selected from the group of:

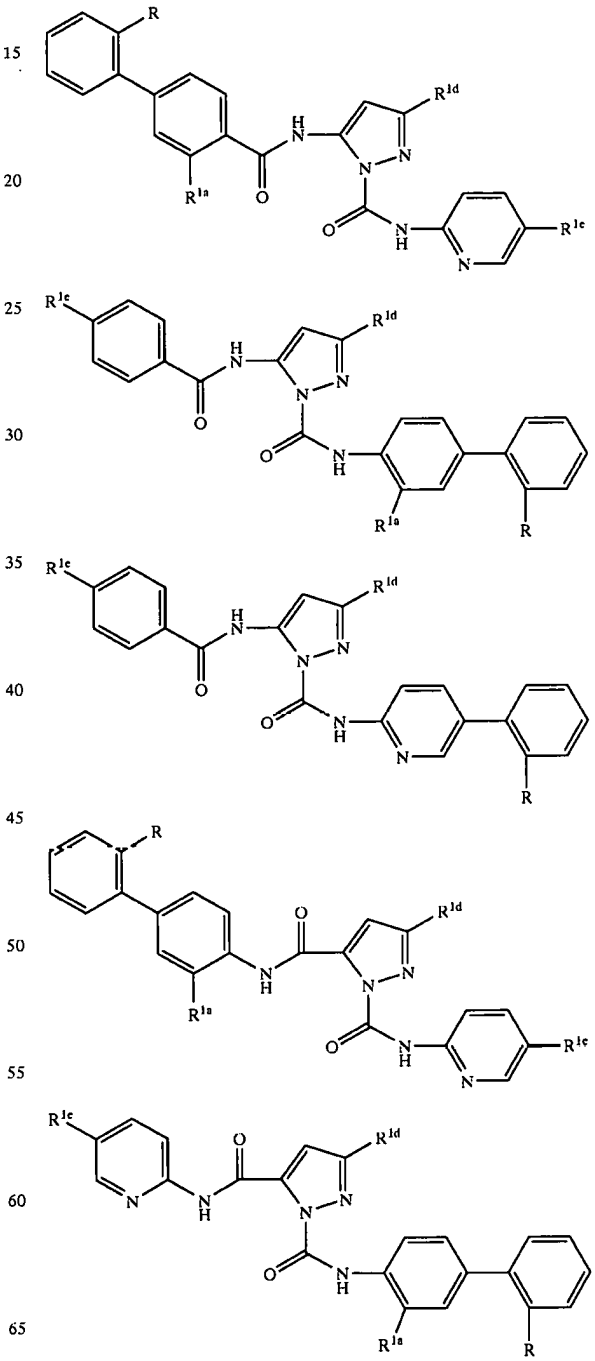
H, —F, —Cl and Br; and

R^{1e} is a member selected from the group of:

H, —F, —Cl, —Br, —NH_2, —CH_2NH_2, —OMe, —OH, —CN, —SO_2Me, —SO_2NH_2.

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



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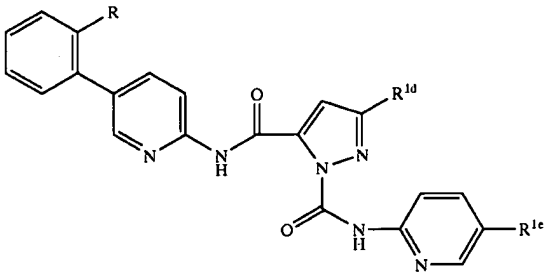

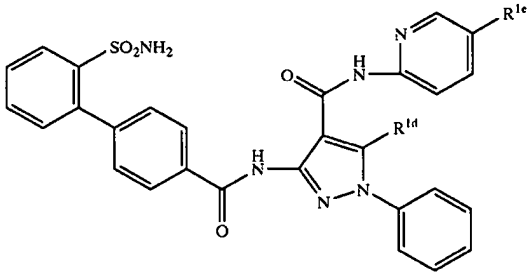

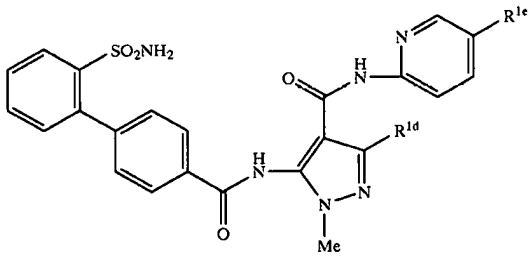

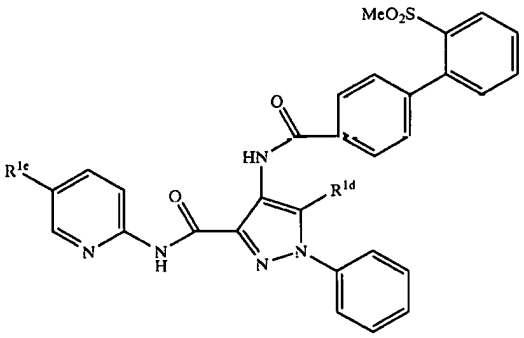

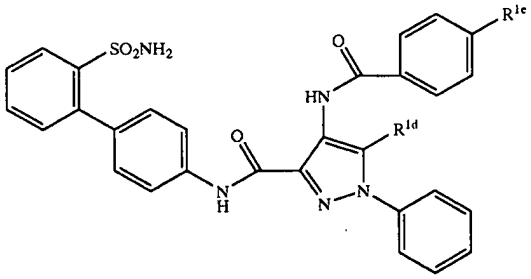

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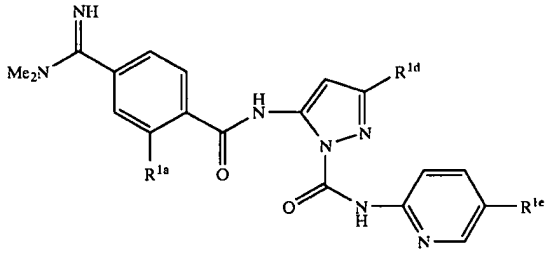
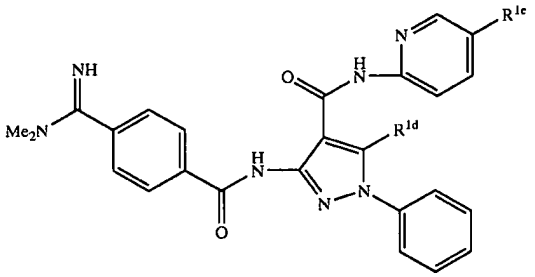




wherein:

R is a member selected from the group of:

$—SO_2NH_2$, $—SO_2Me$, $—CH_2NMe_2$;

R^{1a} is a member selected from the group of:

H, —F, —Cl, —Br;

R^{1d} is a member selected from the group of:

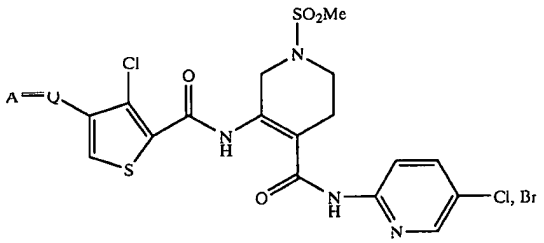
H, —F, —Cl, —Br, —CN, CF_3, $—CH_3$, $—SO_2NH_2$, $—SO_2Me$; and

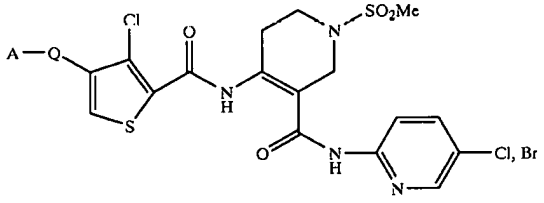
R^{1e} is a member selected from the group of:

—Cl, —Br,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

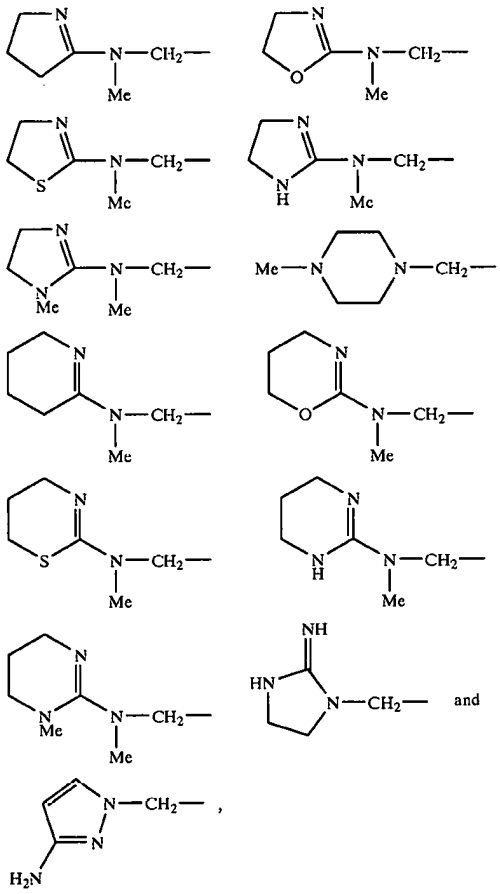
The invention provides compound of formula Ib, as described above, having the following structure:





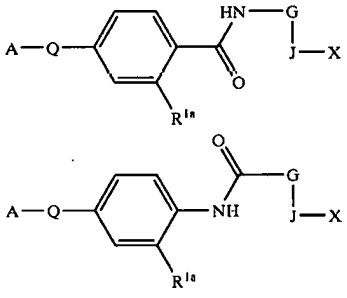
wherein:

A-Q taken together are a member selected from the group consisting of:



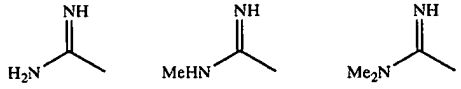
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



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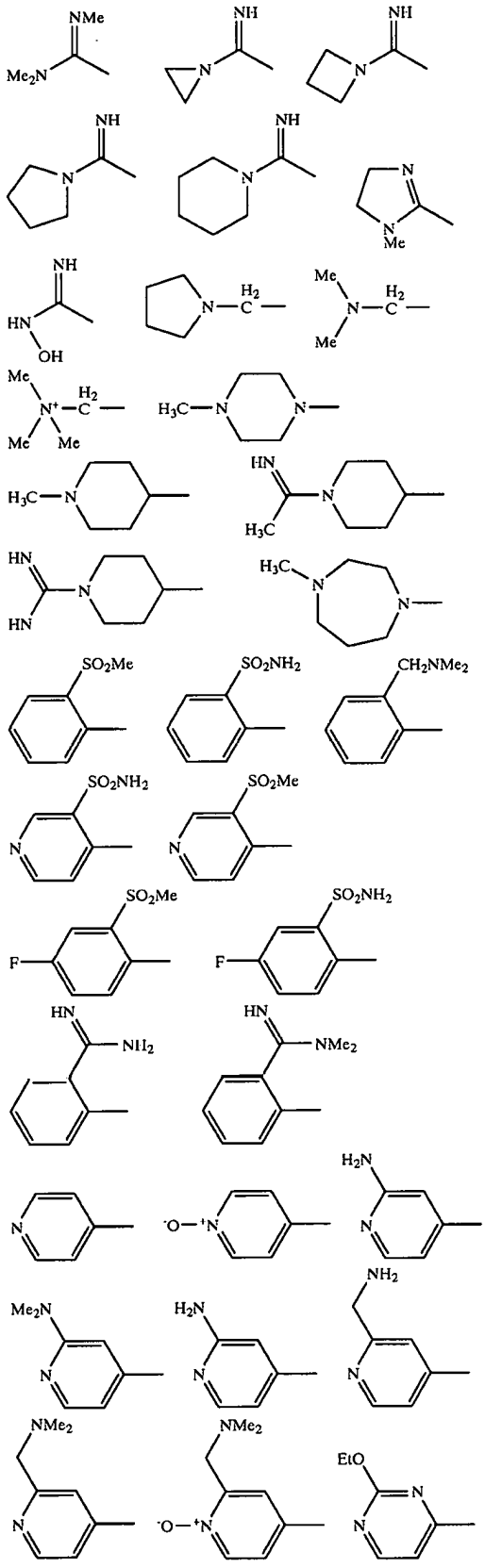

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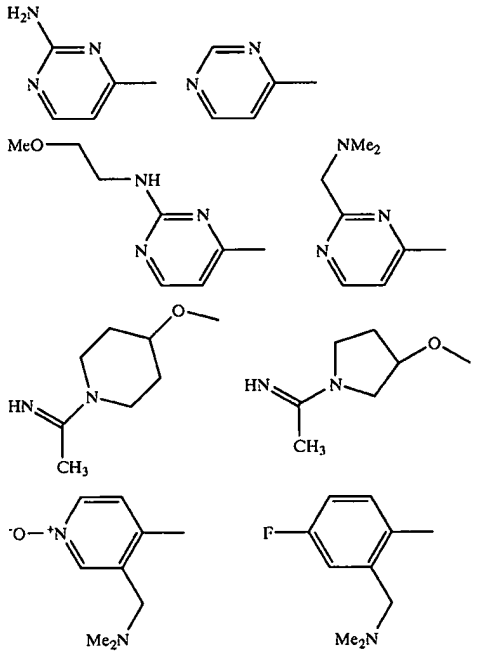
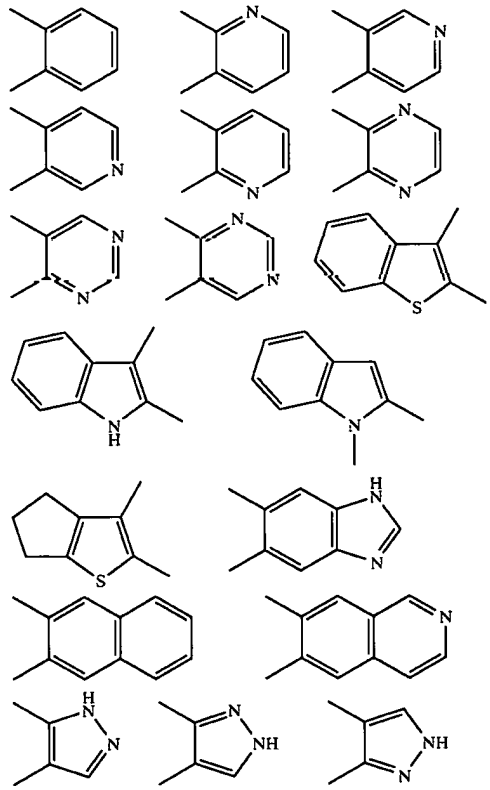


R^{1a} is a member selected from the group consisting of:

H, —F, —Cl and Br;

G is a member selected from the group consisting of:



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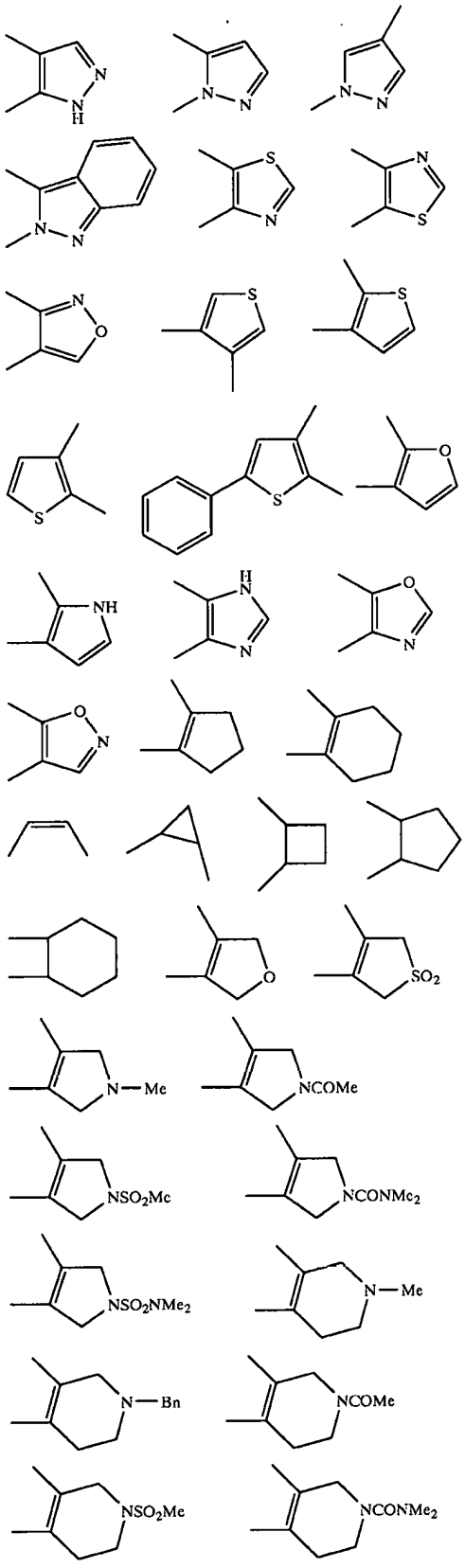

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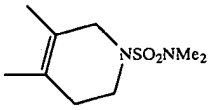
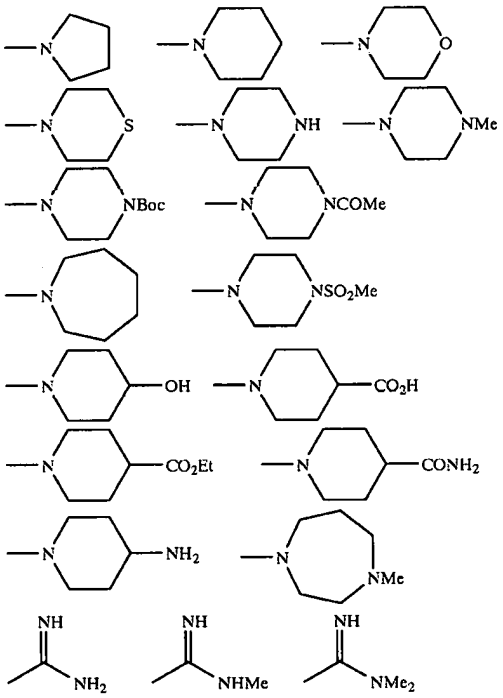


wherein each G group is substituted by 0–4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

H, —Me, —F, —Cl, —Br, aryl, heteroaryl, —NH_2, —NMe_2, —NHMe, —$NHSO_2Me$, —NHCOMe, —CH_3, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH2COOH, —N(Me)CH2CONH2, —N(Me)CH2CH2NMe2, —N(Me)CH2CH2OMe, —NHCH2CH2OMe,



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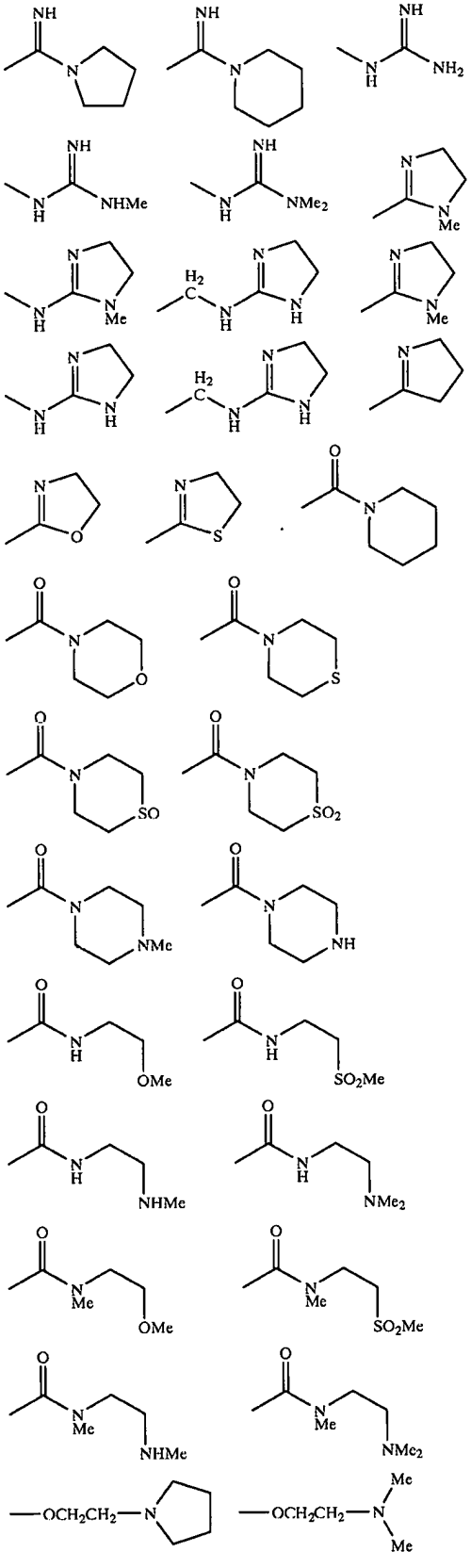

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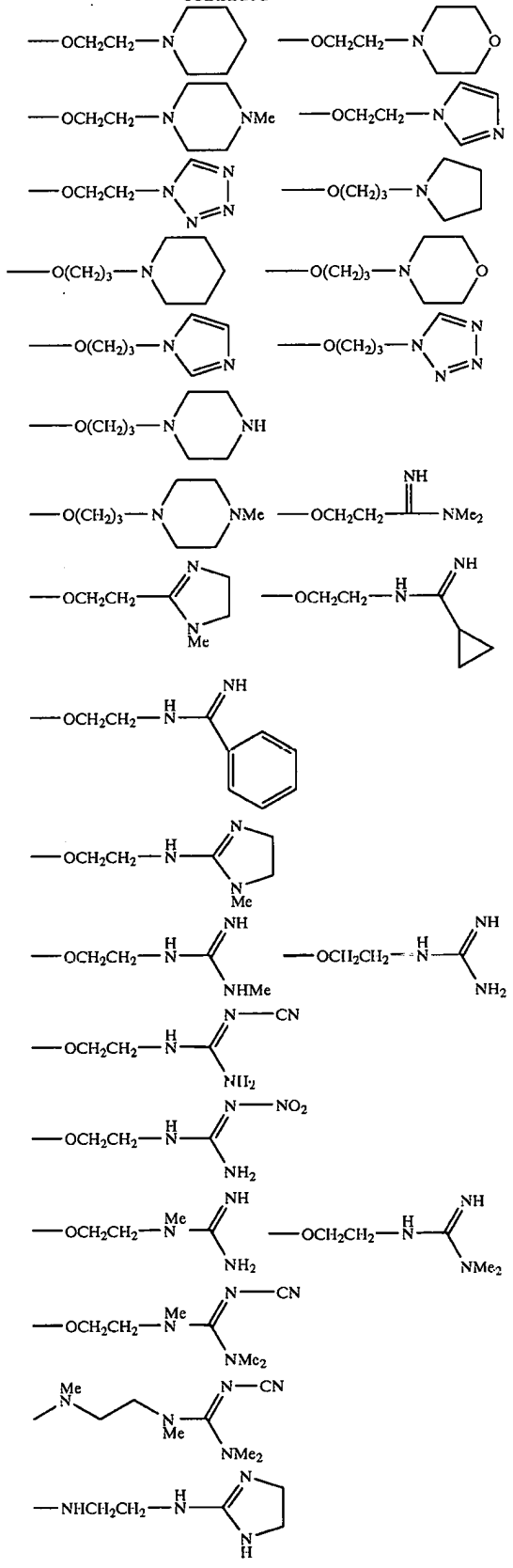

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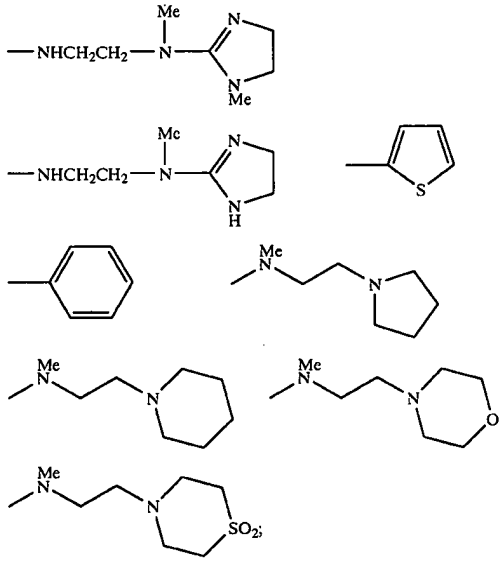
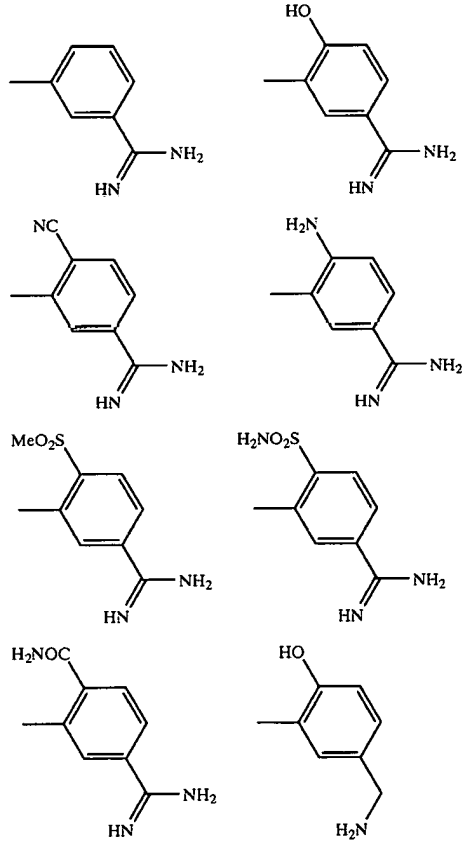


J is a member selected from the group consisting of:

—CONH—, —NHCO—, —O—, —NH—, —NMe—, —CONMe—, —NMeCO—; and

X is a member selected from the group consisting of:



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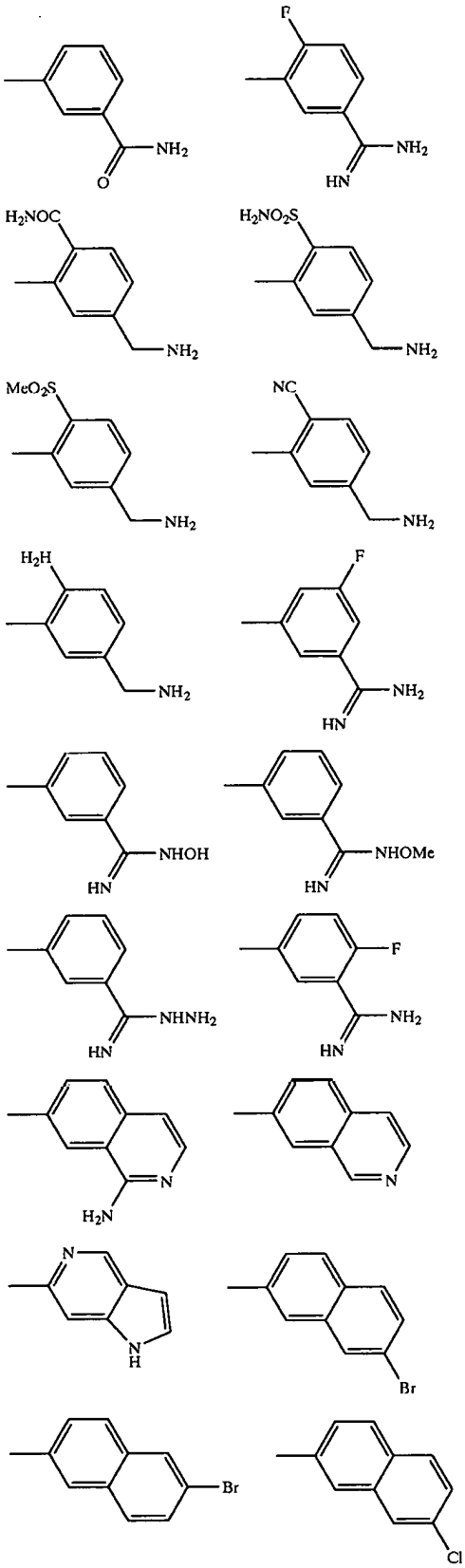

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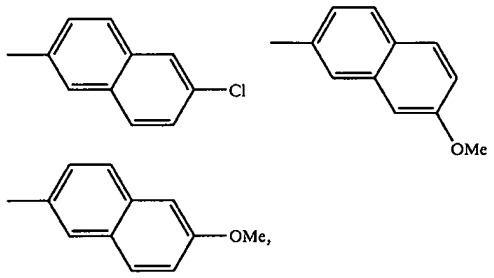
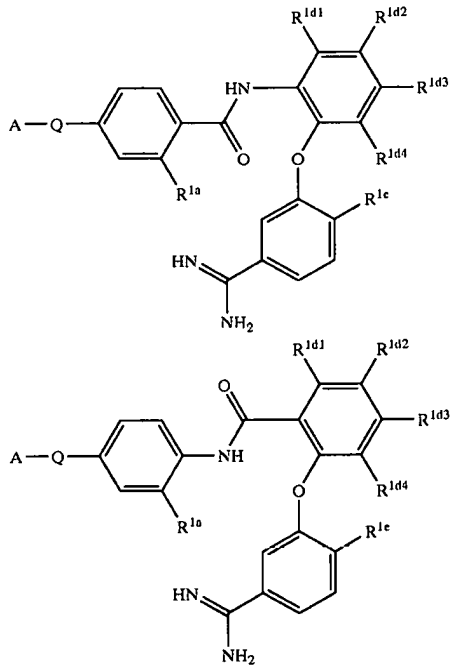


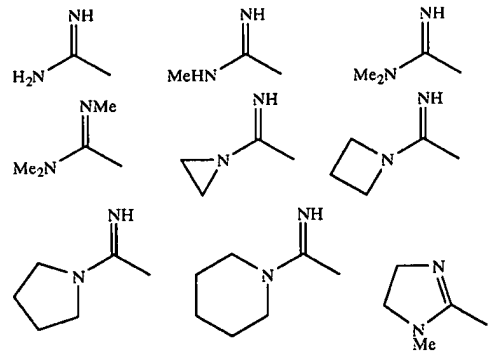
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group of:



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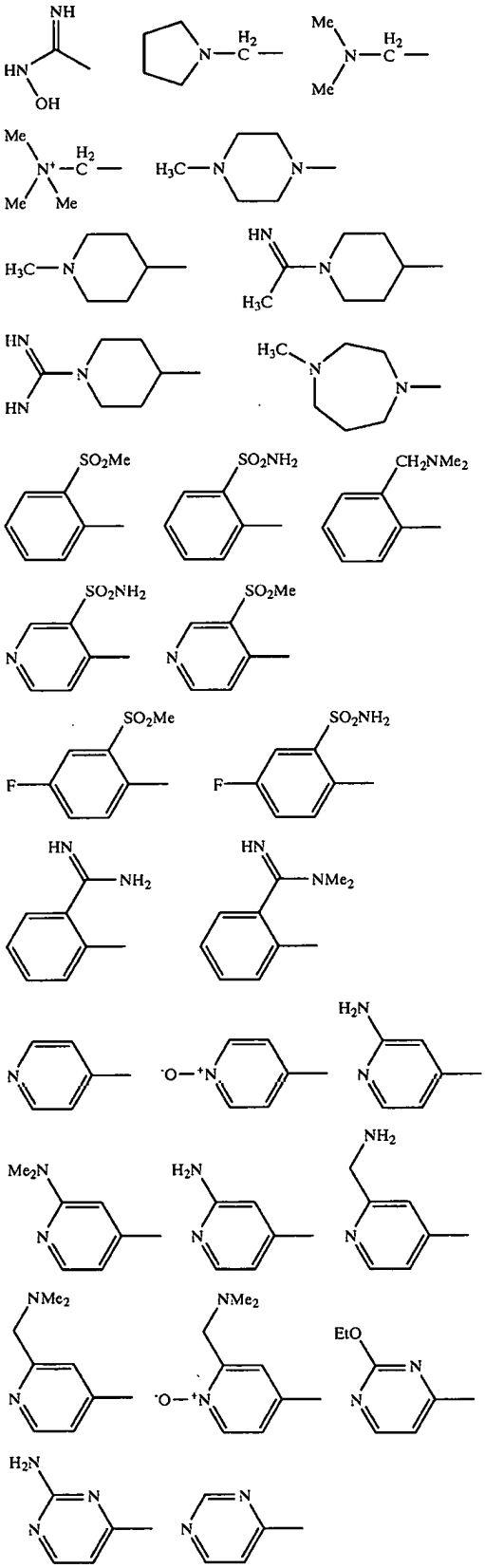

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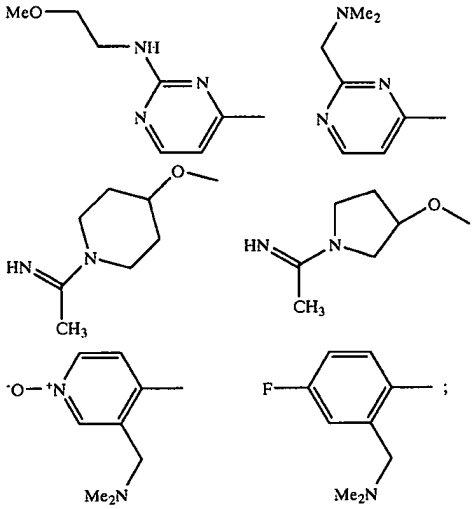
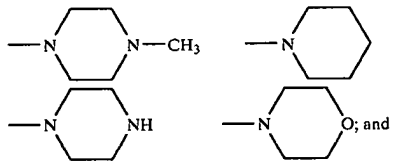


R^{1a} is a member selected from the group of:

H, —F, —Cl, —Br;

R^{1d1}, R^{1d2}, R^{1d3} and R^{1d4} is independently a member selected from the group of:

H, —F, —Cl, —Br, —NO_2, —NH_2, —NHMe, —NMe_2, —NHAc, —$NHSO_2Me$, —SO_2Me, —CO_2H, —CO_2Me, —OH, —OMe, —N(Me)CO2H, —N(Me) CO2Et and

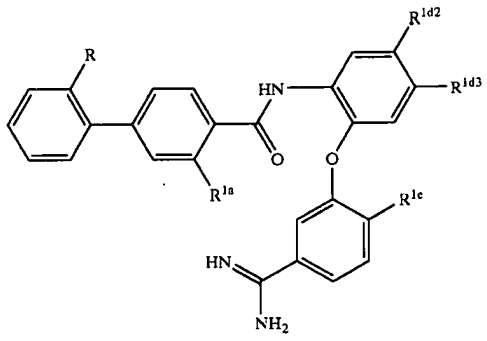


R^{1e} is a member selected from the group of:

H, —OH,

and all pharmaceutically acceptable isomers,salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



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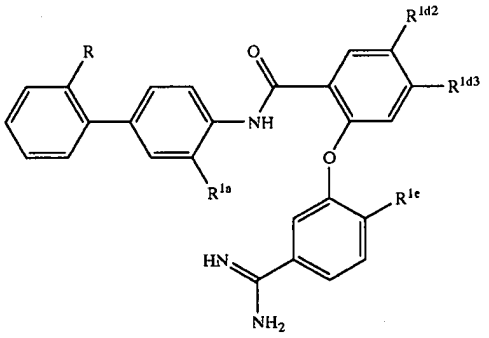
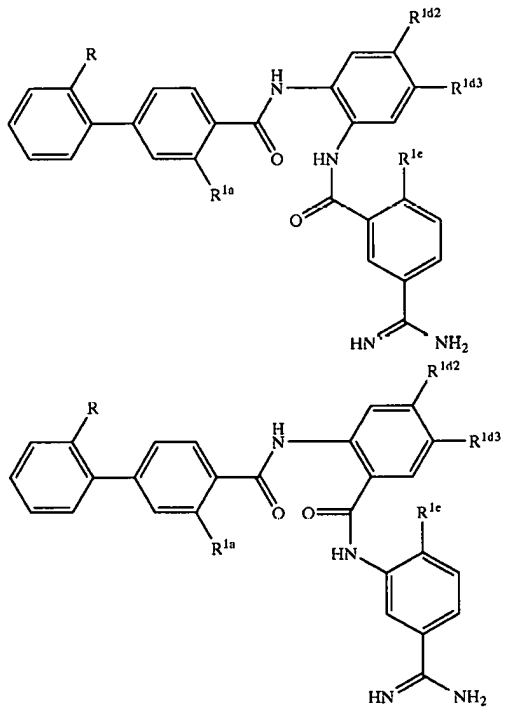


R is a member selected from the group of:
—SO_2Me, —SO_2NH_2, —CH_2NH_2, —$CH_2N(CH_3)_2$;
R^{1a} is a member selected from the group of:
H, —F;
R^{1d2} and R^{1d3} is independently a member selected from the group of:
H, —F, —Cl, —Br, —NO_2, —NH_2, —NHMe, —NMe_2, —NHAc, —$NHSO_2Me$, —SO_2Me, —CO_2H, —CO_2Me, —OH, —OMe; and
R^{1e} is a member selected from the group of:
H, —OH,
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

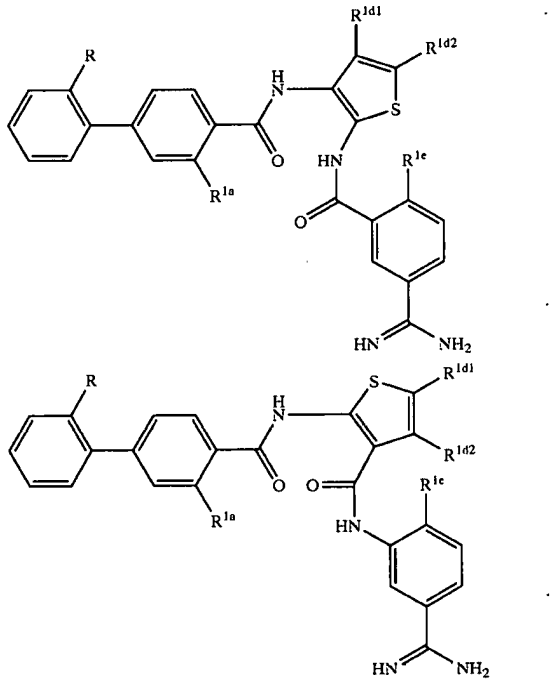
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R is a member selected from the group of:
—SO_2Me, —SO_2NH_2, —CH_2NH_2, —$CH_2N(CH_3)_2$;
R^{1a} is a member selected from the group of:
H, —F;
R^{1d2} and R^{1d3} is independently a member selected from the group of:
H, —F, —Cl, —Br, —NO_2, —NH_2, —NHMe, —NMe_2, —NHAc, —$NHSO_2Me$, —SO_2Me, —CO_2H, —CO_2Me, —OH, —OMe; and
R^{1e} is a member selected from the group of:
H, —OH,
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



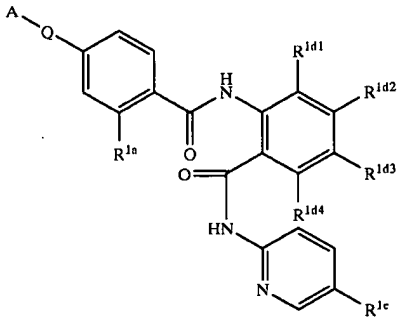
R is a member selected from the group of:
—SO_2Me, —SO_2NH_2, —CH_2NH_2, —$CH_2N(CH_3)_2$;
R^{1a} is a member selected from the group of:
H, —F;
R^{1d1} and R^{1d2} is independently a member selected from the group of:
H, —F, —Cl, —Br, —OMe; and
R^{1e} is a member selected from the group of:
H, —OH,
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The following preferred embodiments of the present invention illustrate compounds wherein the central aromatic ring structure is divalent phenylene, however divalent 6 membered heteroaromatic rings having from 1 to 3 nitrogen atoms may be substituted for the bivalent phenylene structure. Further the terminal aromatic ring substituted which is substituted by a R^{1e} group as illustrated below in the preferred embodiments is either a phenyl or a 2-pyridyl group, however other 6 membered heteroaromatic rings having from 1 to 3 nitrogen atoms can be substituted for either the phenyl or 2-pyridyl. Moreover, 2 to 3 additional R^{1e} groups other than hydrogen may each be independently

substituted for a hydrogen atom attached to a ring carbon on the terminal rings illustrated or substituted for the illustrated terminal ring structure.

A preferred embodiment of the invention provides a compound of formula VIII:

(VIII)

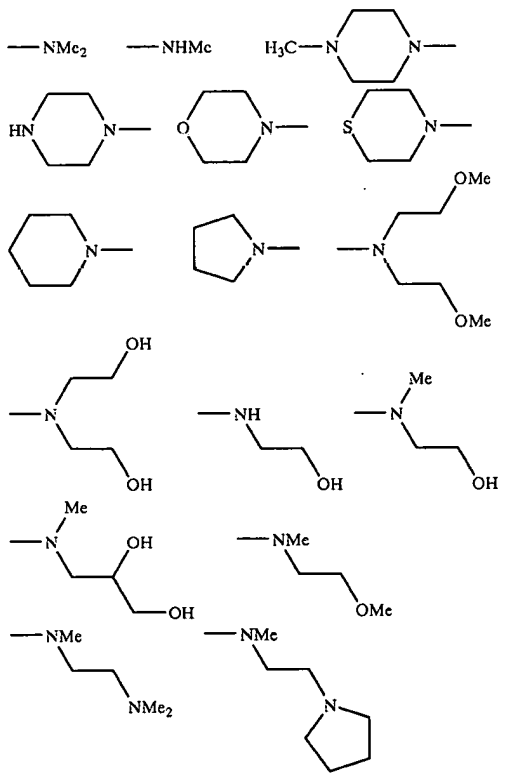


wherein:

R^{1a} is a member selected from the group of H, —F, —Cl and Br;

R^{1d2} and R^{1d4} are each H or F;

R^{1d1} and R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH, —OMe, —OCF_3, $OCHF_2$, OCH_2F, —NH_2, —NMe_2, —OCH_2COOEt, —OCH_2COOH, —$N(Me)CH_2COOH$, —N(Me)COOEt, and,



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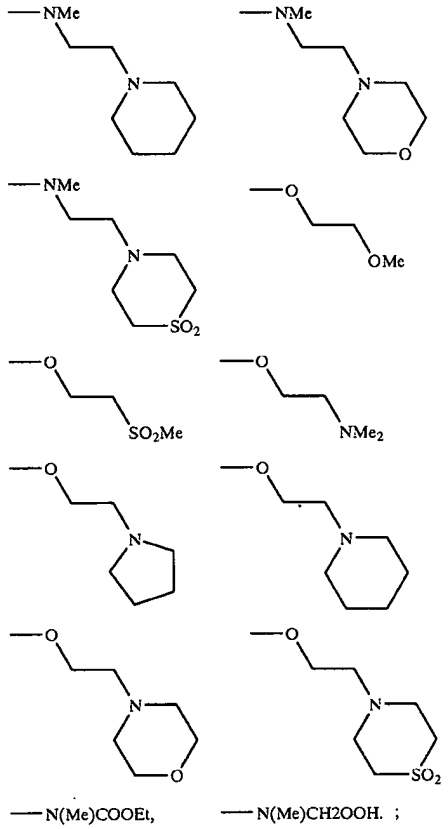
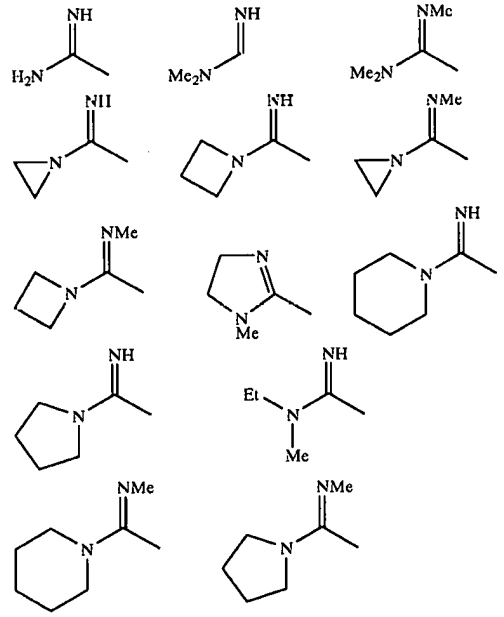


—N(Me)COOEt, —N(Me)CH2OOH. ;

R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe,

A-Q is a member selected from the group consisting of:



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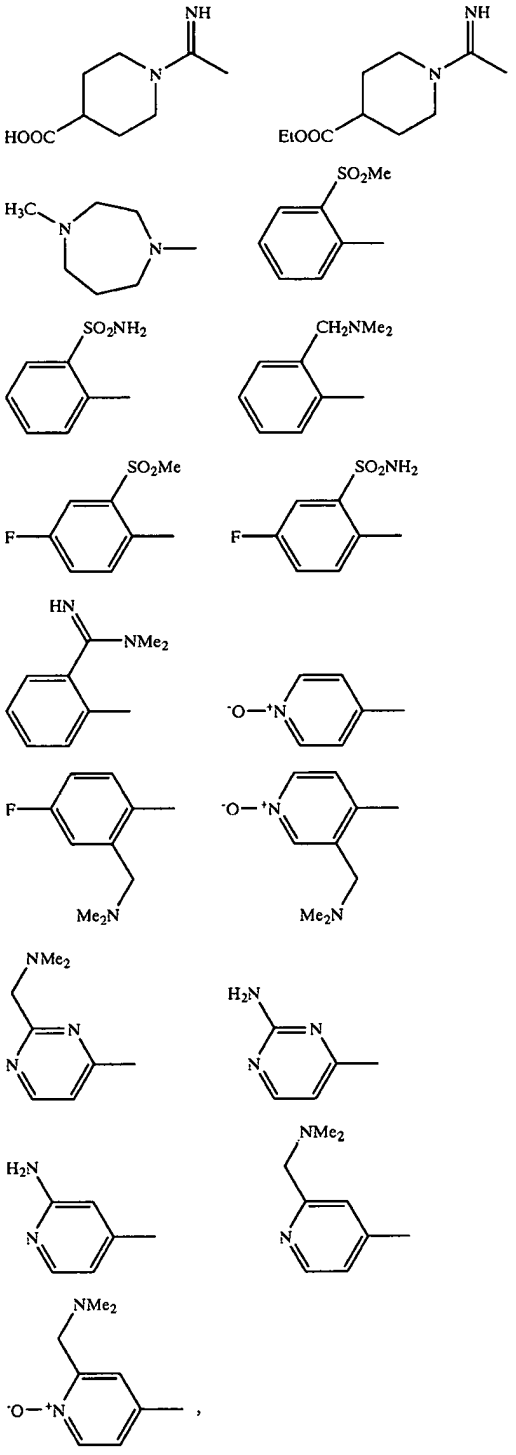
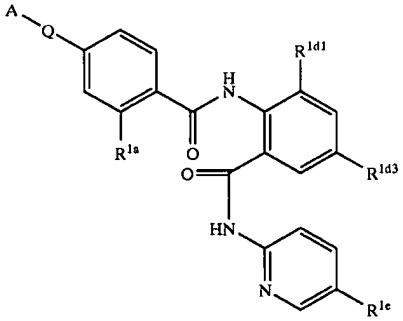


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

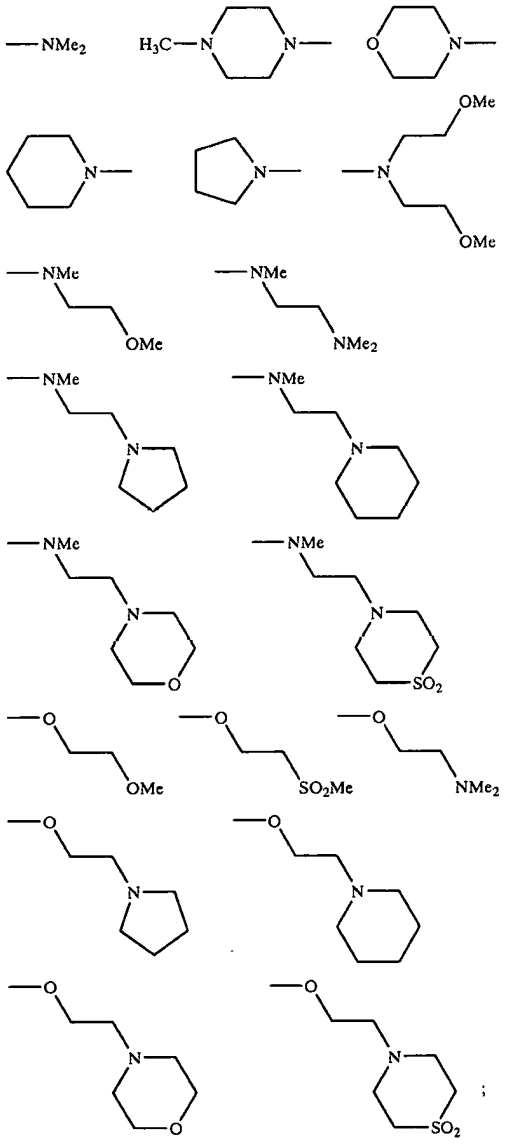
Another prefer red embodiment provides a compound of formula VIII having the following structure:



wherein:

R^{1a} is a member selected from the group of H, or —F;

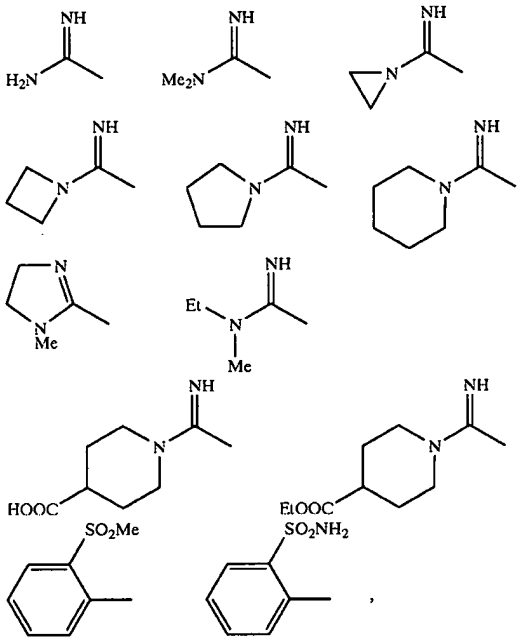
R^{1d1} is each independently a member selected from the group of H, —Cl, —OMe, —NMe_2, —OCH_2COOEt, —OCH_2COOH, —$N(Me)CH_2COOH$, —N(Me)COOEt,



R^{1d3} are independently a member selected from the group of H, —Cl, —Br, —F, and —OMe;

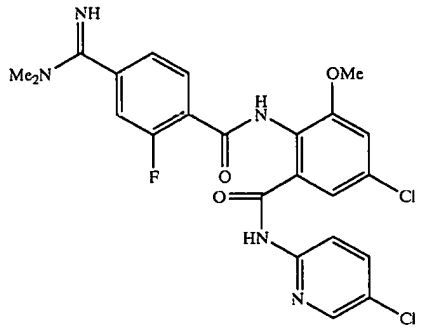
R^{1e} is a member selected from the group of —Cl, and —Br;

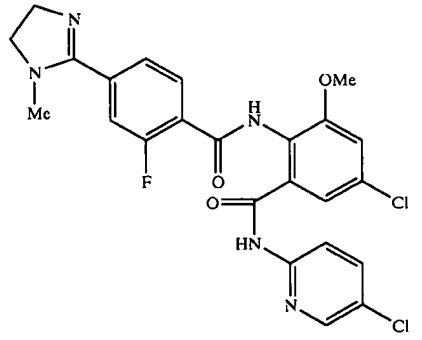
A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment according to the present invention provides an individual compound, which is a member selected from the following structures:





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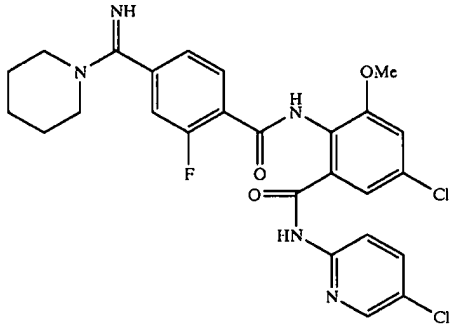

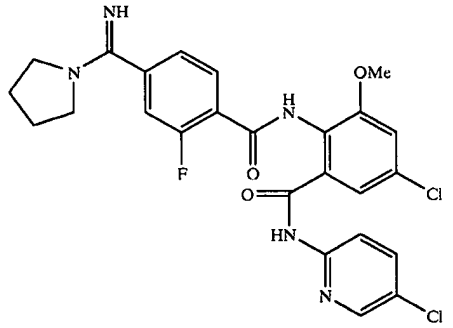

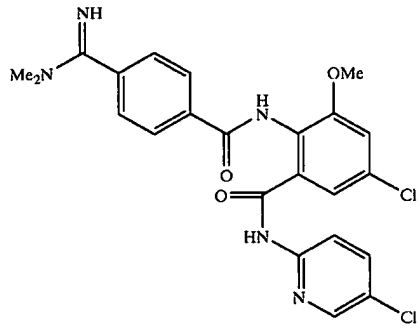

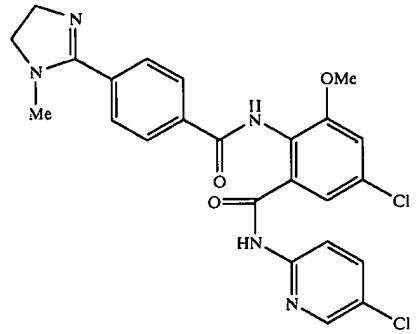

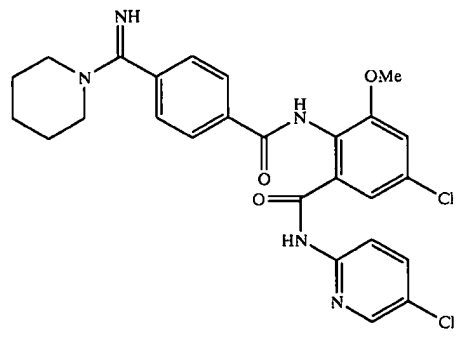

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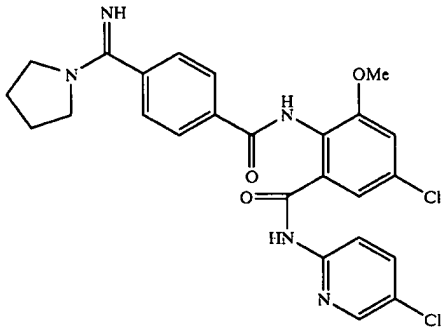

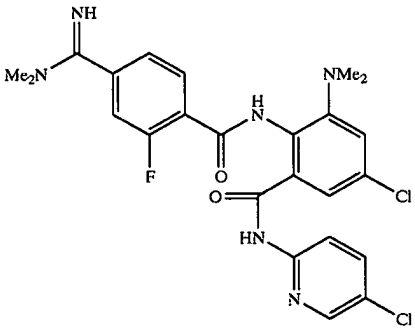

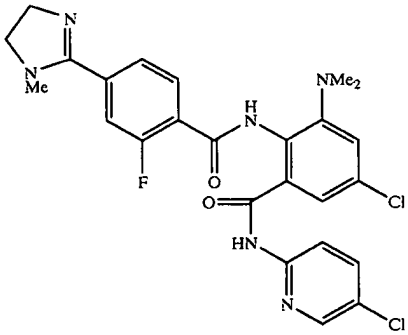

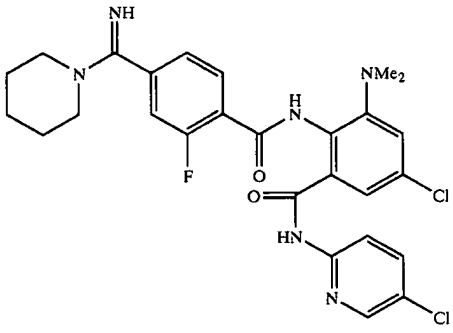

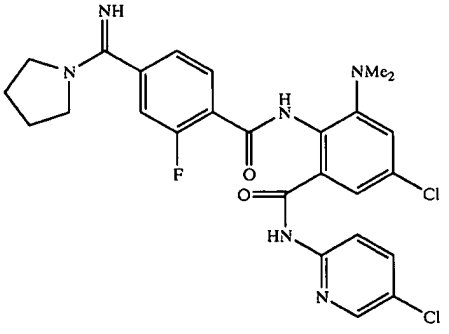

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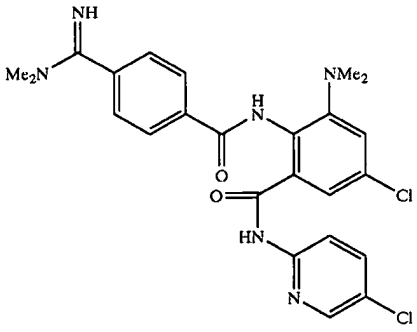

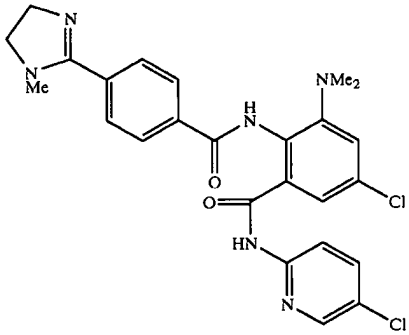

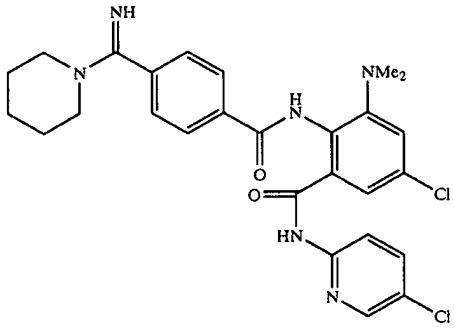

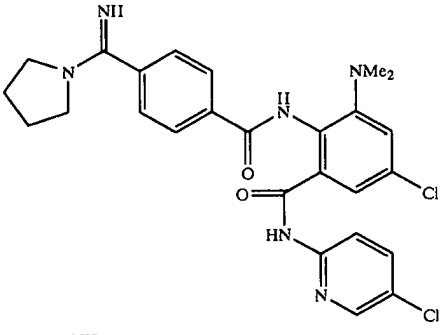

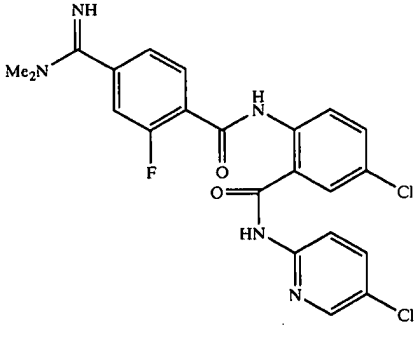

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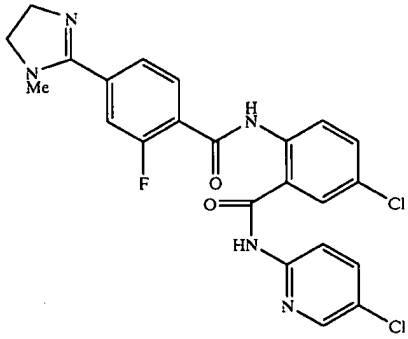

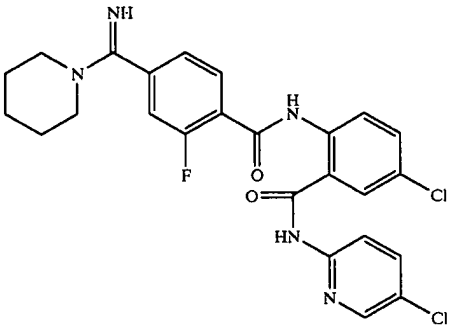

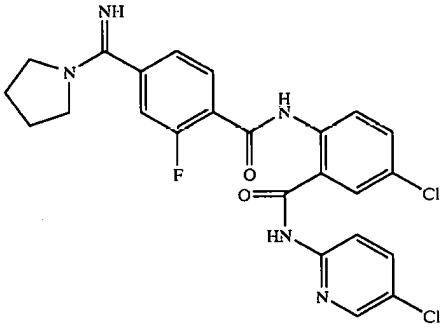

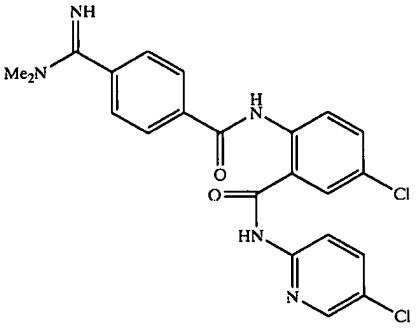

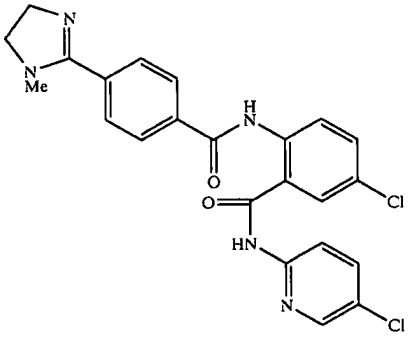

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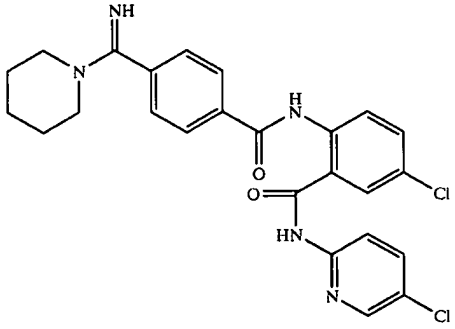

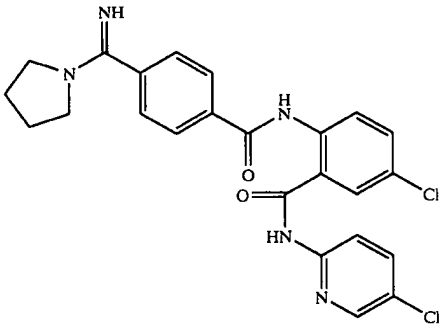

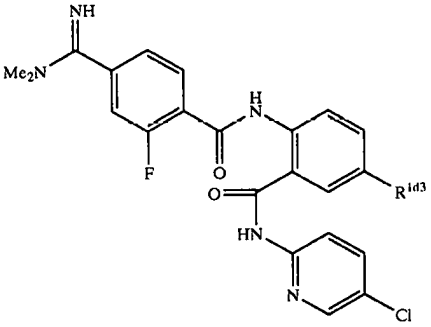

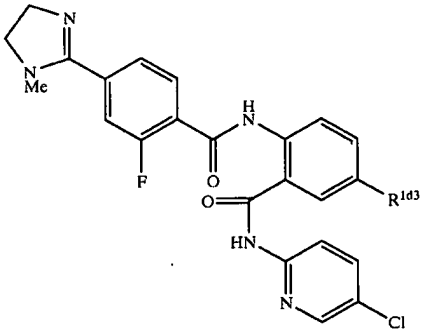

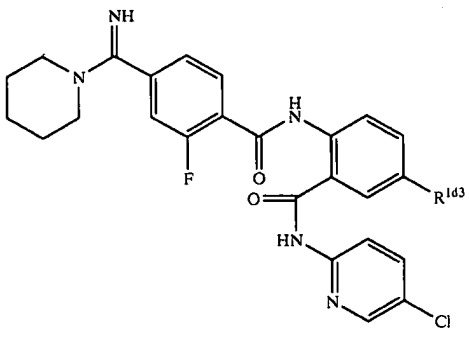

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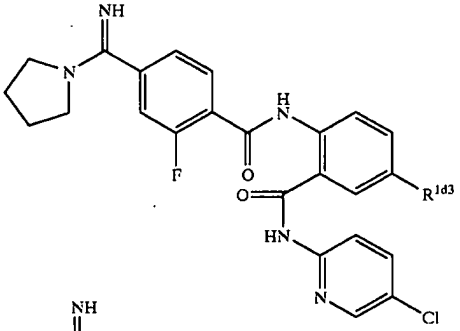
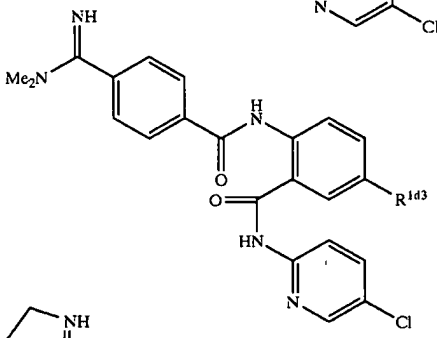
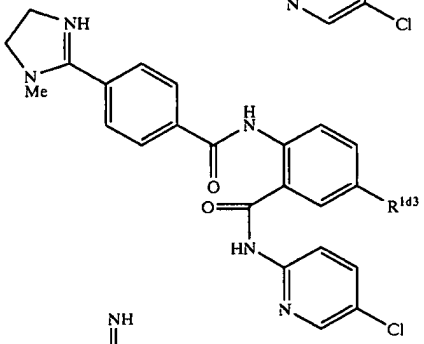
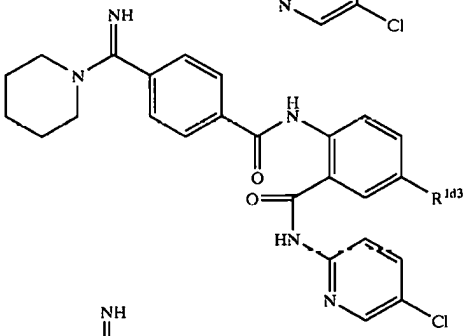
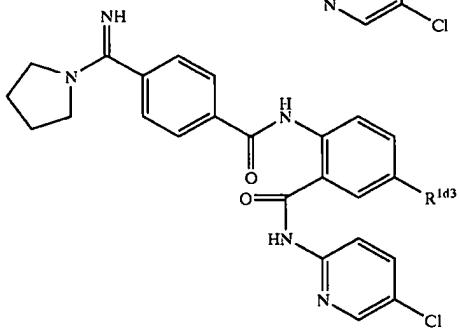










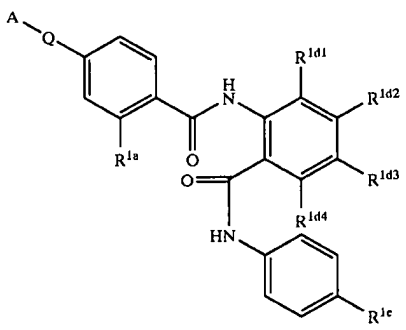
wherein

R^{1d3} is a member selected from the group consisting of: H, —F, —Cl, —Br, —OMe, —OCF_3, —OCF_2H, and —OCF_2H;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

A still further embodiment of the present invention provides a compound according to the formula IX, as follow:

(IX')

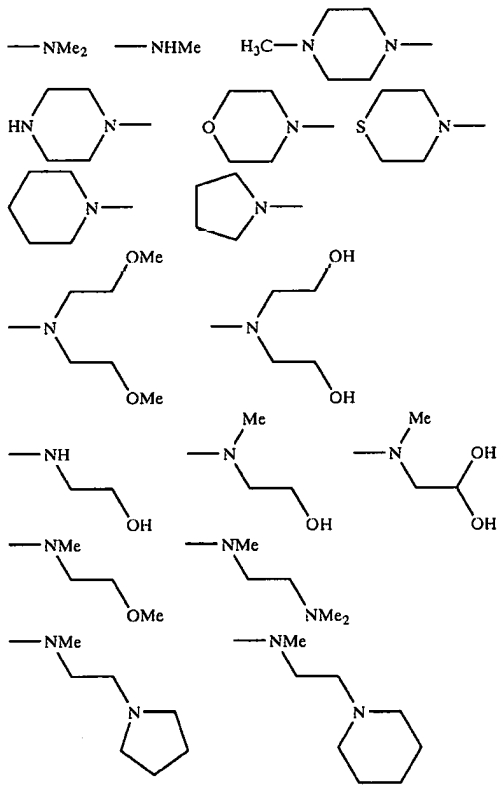


wherein:

R^{1a} is a member selected from the group of H, —F, —Cl and Br,

R^{1d2} and R^{1d4} are each H or F;

R^{1d1} and R^{1d3} are each independently a member selected from the group of H, —Cl, —F, —Br, —OH, —OMe, —OCF_3, $OCHF_2$, OCH_2F, —NH_2, —NMe_2, —OCH_2COOEt, —OCH_2COOH, —$N(Me)CH_2COOH$, —N(Me)COOEt,



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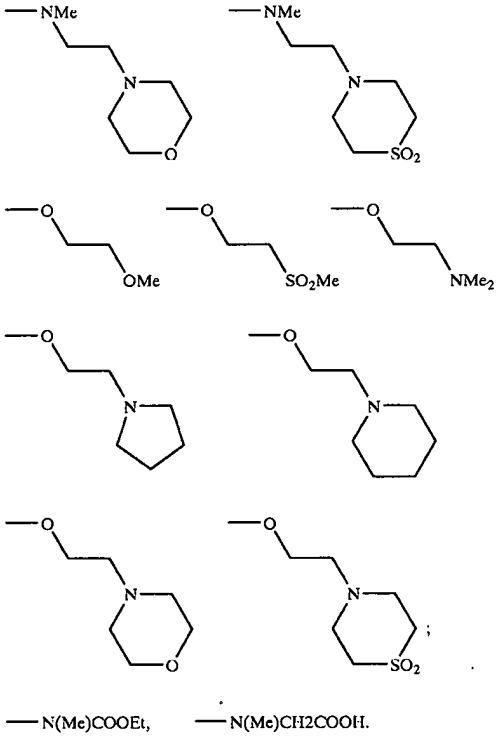
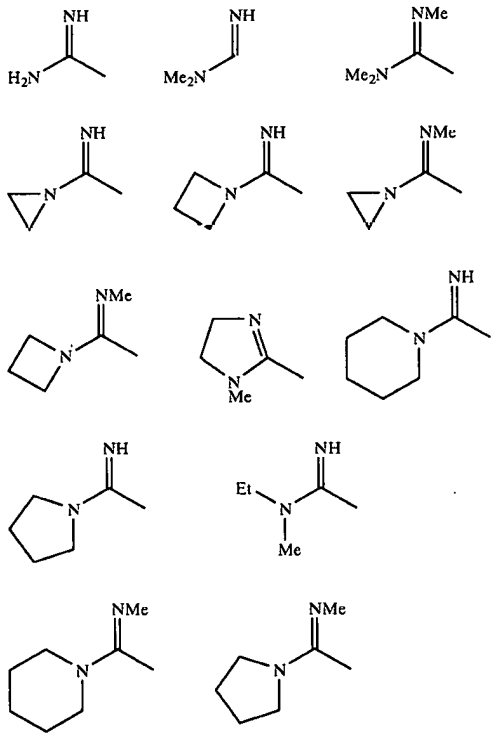


—N(Me)COOEt, —N(Me)CH2COOH.

R^{1e} is a member selected from the group of —F, —Cl, —Br, —OH, —Me and —OMe;

A-Q is a member selected from the group consisting of:



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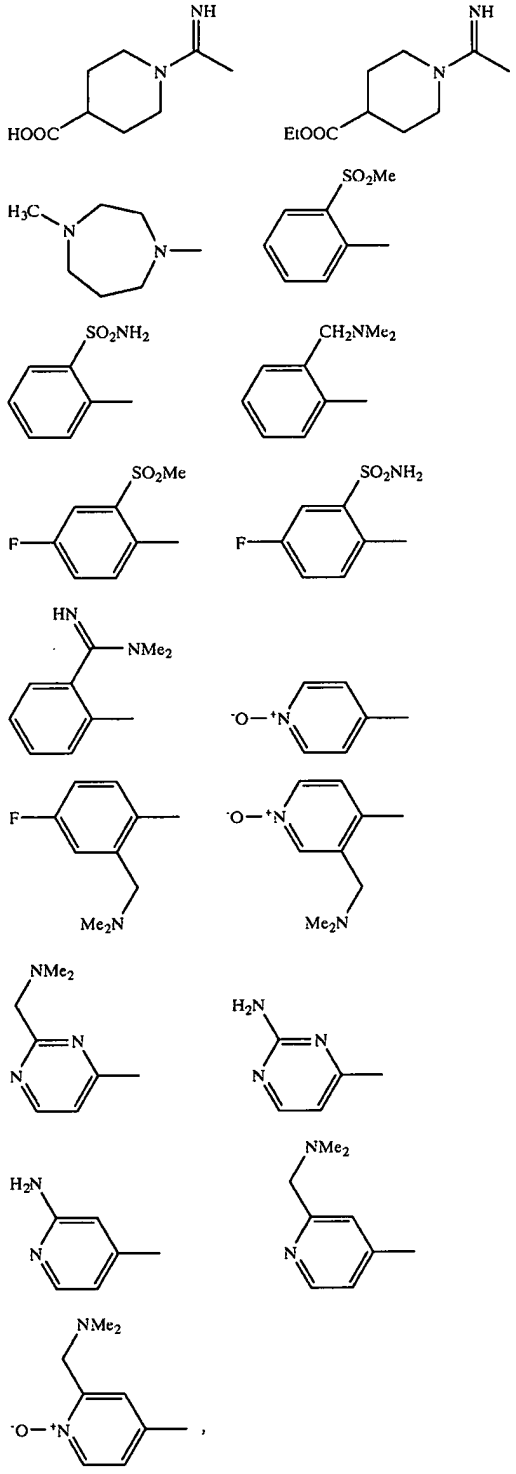
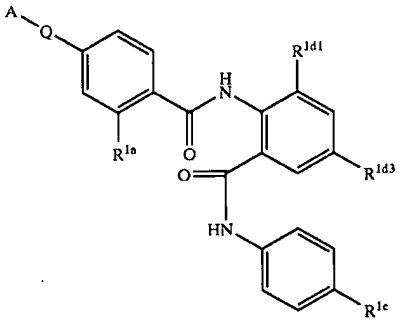


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

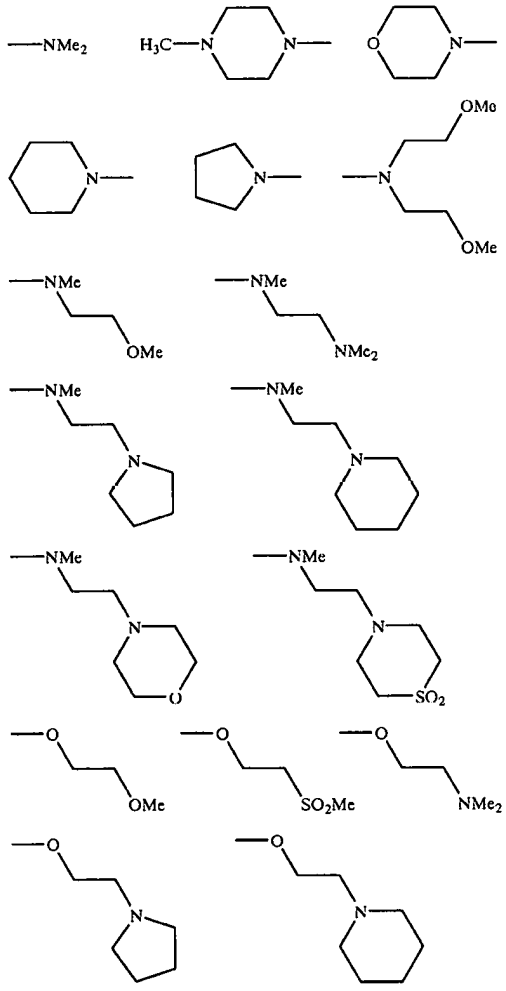
A particularly preferred embodiment of the present invention provides such compounds having the following formula:



wherein:

R^{1a} is a member selected from the group of H, or —F

R^{1d1} is each independently a member selected from the group of H, —Cl, —OMe, —NMe_2, —OCH_2COOEt, —OCH_2COOH, —$N(Me)CH_2COOH$, —N(Me)COOEt, and,



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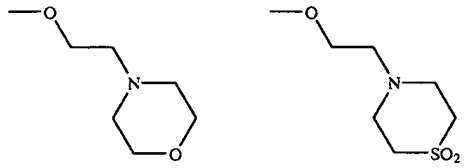
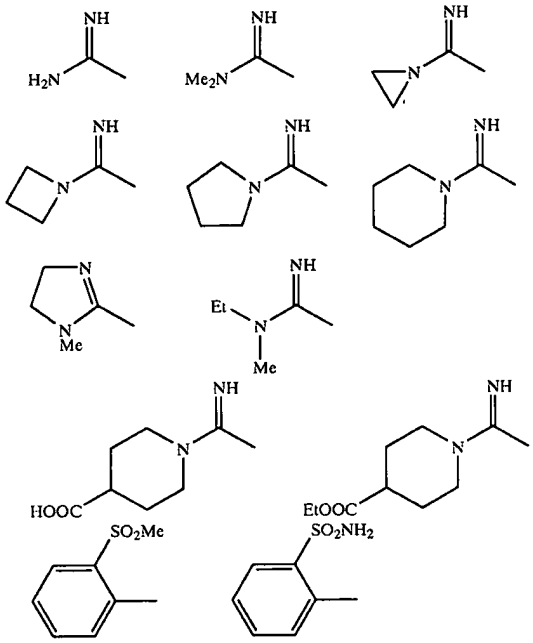


R^{1d3} are independently a member selected from the group of H, —Cl, —Br, —F, and —OMe,

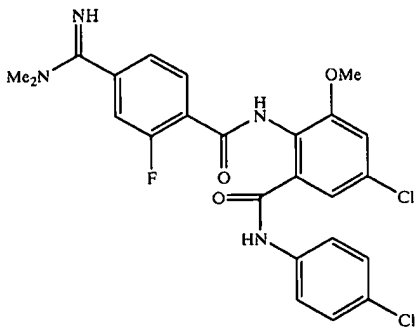
R^{1c} is a member selected from the group of —Cl, and —Br,

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

A still further embodiment of the present invention provides an individual compound which is a member selected from the following structures:



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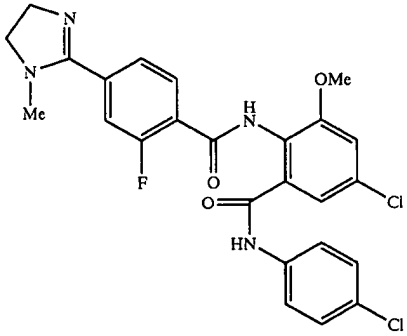

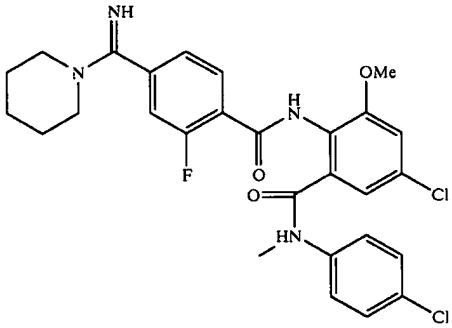

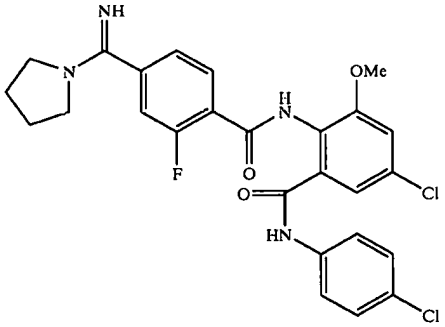

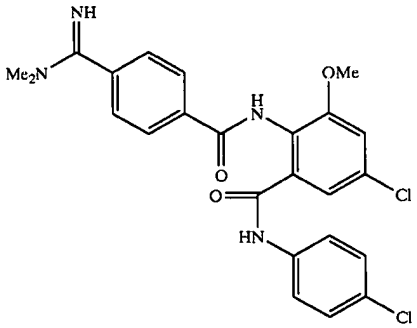

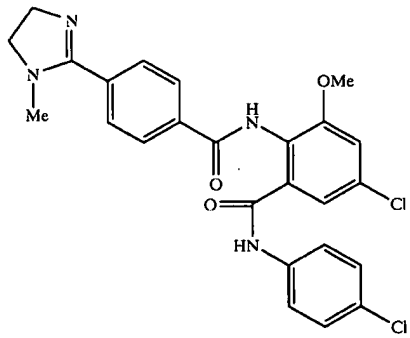

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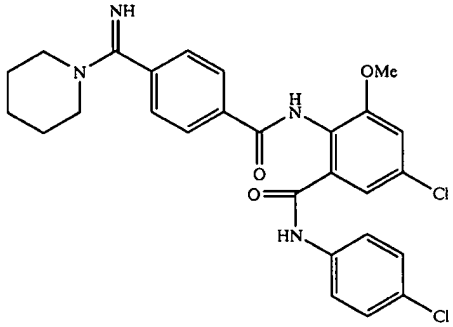

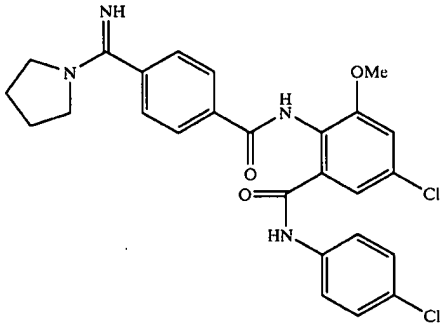

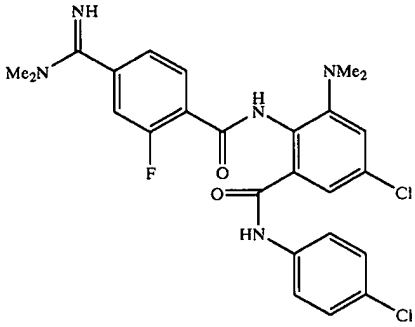

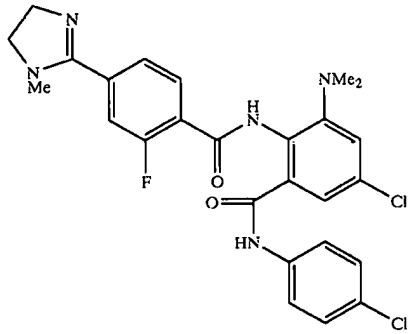

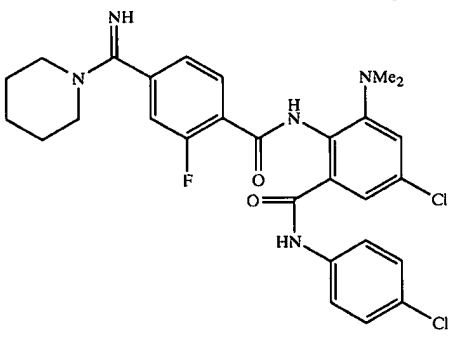

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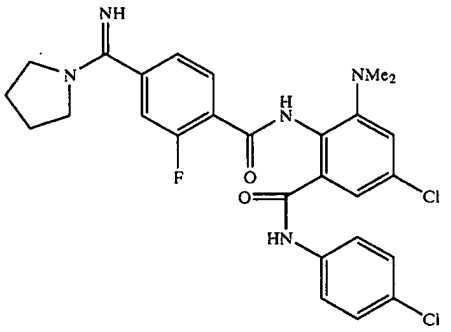

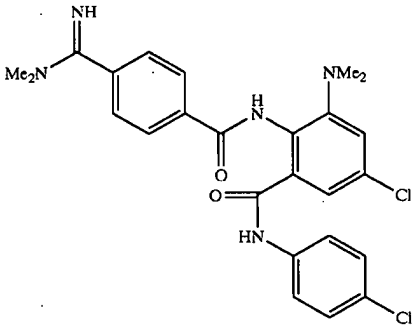

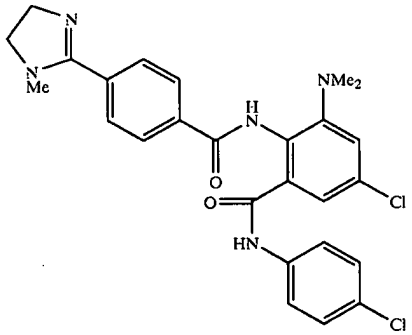

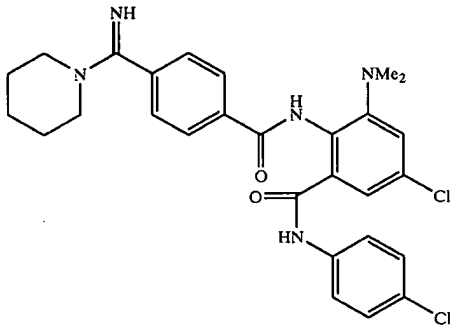

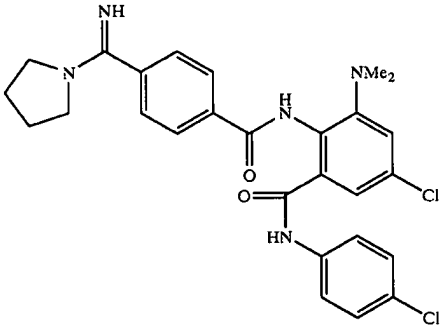

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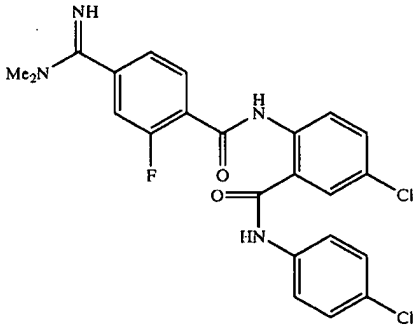

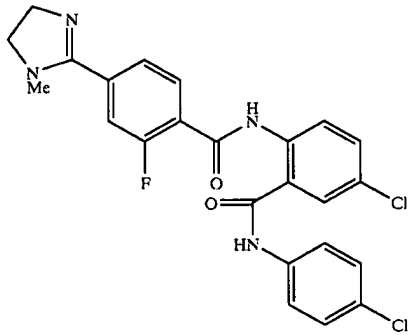

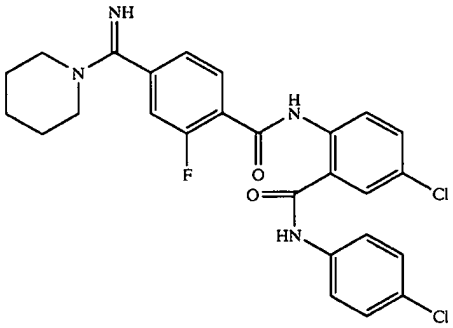

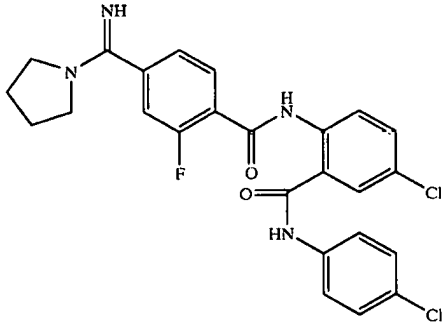

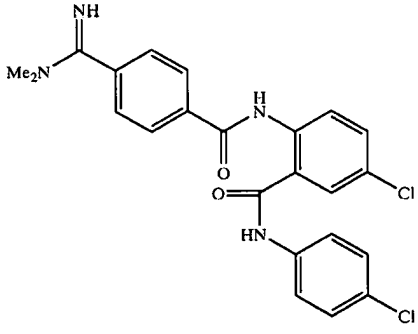

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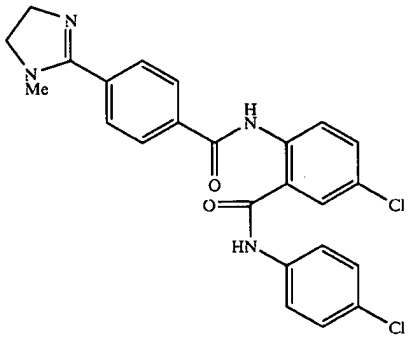

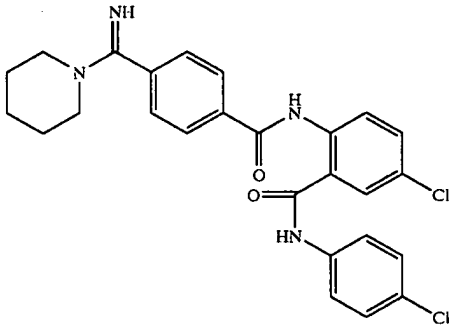

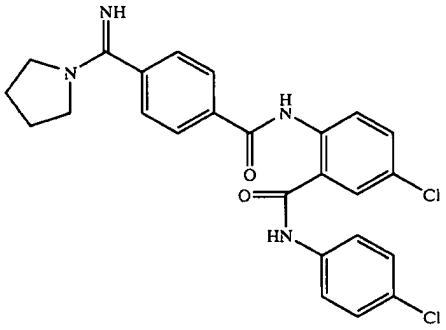

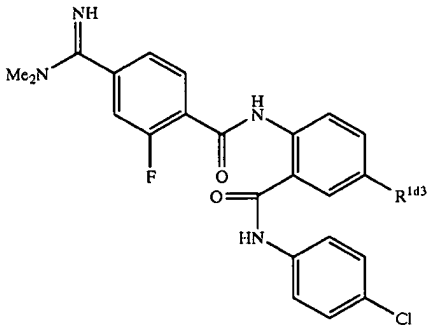

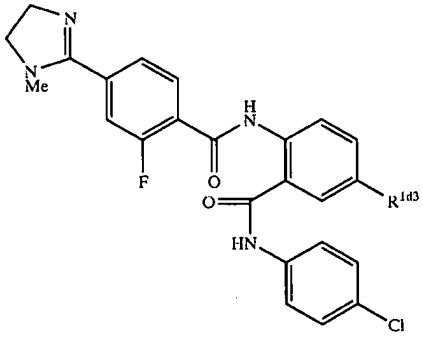

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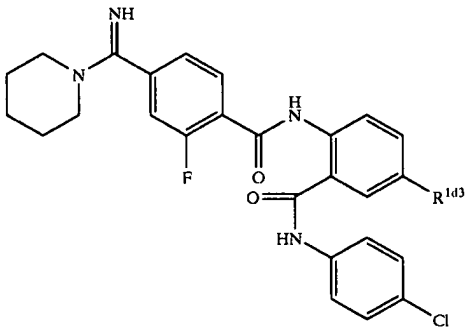

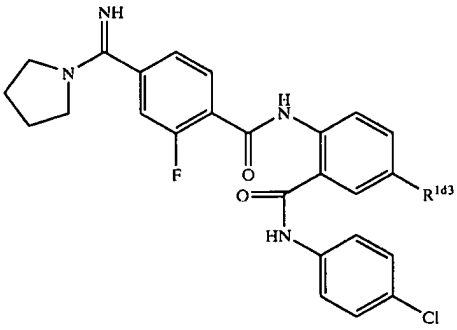

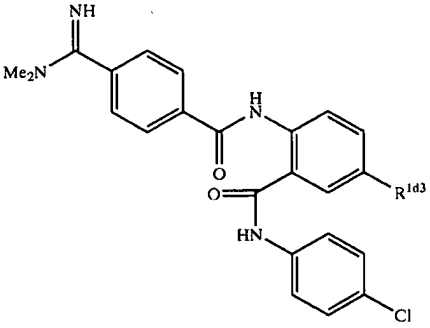

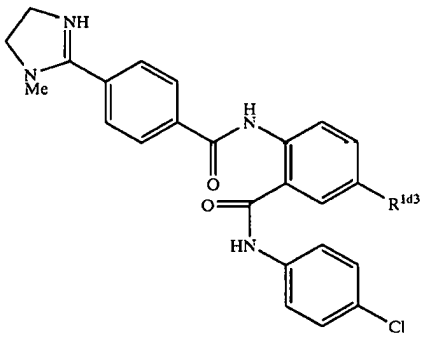

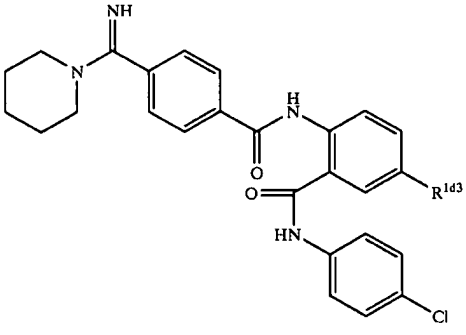

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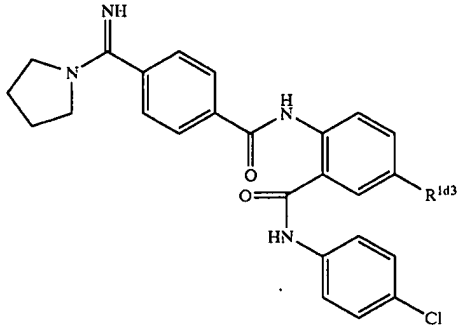


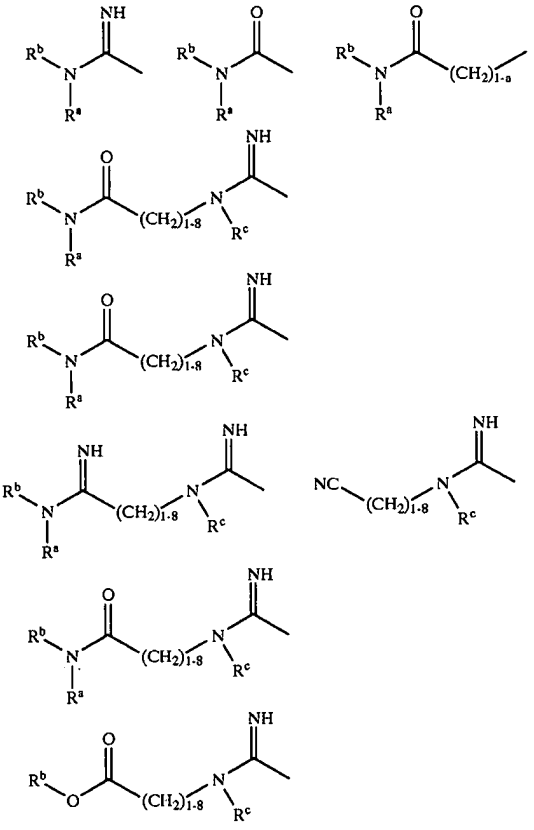
wherein

R^{1d3} is a member selected from the group consisting of:

H, —F, —Cl, —Br, —OMe, —OCF_3, —OCF_2H, and —OCF_2H,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment of the present invention provides compounds according to the invention as illustrated herein, wherein the A-Q- substituent is an amidinosubstituent, the amine portion of which is a cyclized amine heterocyclic ring, preferably a saturated cyclized amine heterocyclic ring, and the cyclized amine ring is substituted by 1–3 members. Examples of such A-Q substituents include but are not limited to:



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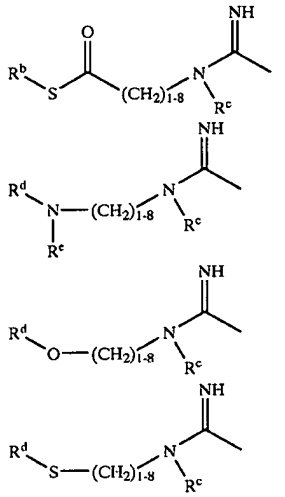


wherein each of R^a, R^b, R^c, R^d and R^e is independently a member selected from the group consisting of C_1–C_8 alkyl, C_2–C_8 alkenyl, C_1–C_8 acyl and C_1–C_8 acyl C_1–C_8 alkyl ester, and the Ra and Rb groups together with the nitrogen atom to which they are both attached may be cyclized to form a C_3–C_8 heterocylic ring having from 1 to 4 additional hetero ring atoms selected from O, N and S, and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment is an embodiment wherein the amidino groups illustrated above as substituents for the cyclized amine heterocyclic ring are instead form an acyclic amidino A-Q group and and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Such compounds are formed by reacting the appropriate acyclic amine or cycliczed amine with an amidino group or with a thioimino group wherein the remainder of the structures D—E—G—J—X are defined as in formula I or as in a preferred D—E—G—J—X structure illustrated in a preferred embodiment herein. Other ways to produce such compound structures will be apparent to an ordinary praticitioner in this field upon consideration of the description herein and the illustrated preferred embodiments.

This invention also encompasses all pharmaceutically acceptable isomers. salts, hydrates, solvates, and prodrug derivatives of the preferred compounds. In addition, the preferred compounds can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates, solvates, and prodrug derivatives of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or

in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active in vivo, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7–9, 21–24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352–401, Academic Press, San Diego, Calif., 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other Antithrombotic, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side effects. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or in vitro.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the in vitro protease activity assays and in vivo studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A. R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates

including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3–11, more preferably 5–9 and most preferably 7–8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxypropyl-methacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either in vitro or in vivo methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, Bodanszky, "The Principles of Peptide Synthesis", Hafner, et al., Eds., Springer-Verlag, Berlin, 1984.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, etal., Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Compounds according to the invention can be synthesized utilizing procedures well known in the art. The reaction

products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington 's Pharmaceutical Sciences*, Mack Publishing Co., (A. R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropyl-methacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either in vitro or in vivo methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of admin-

istration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or in vitro.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiutis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

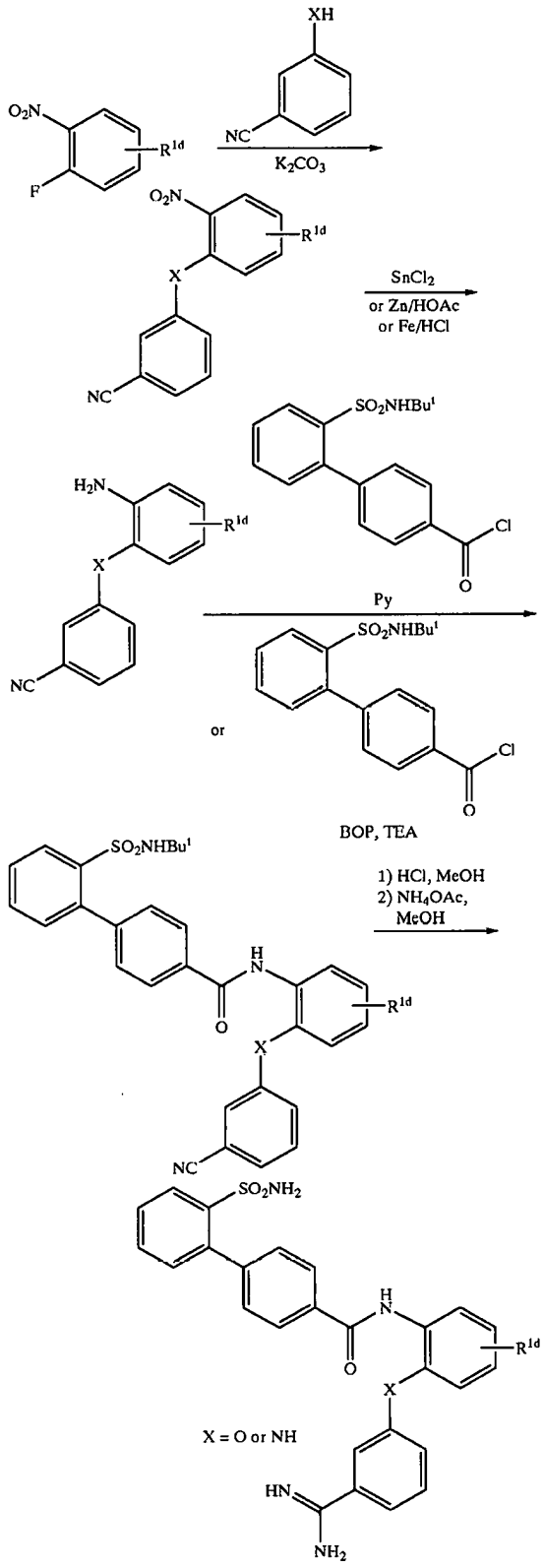
Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

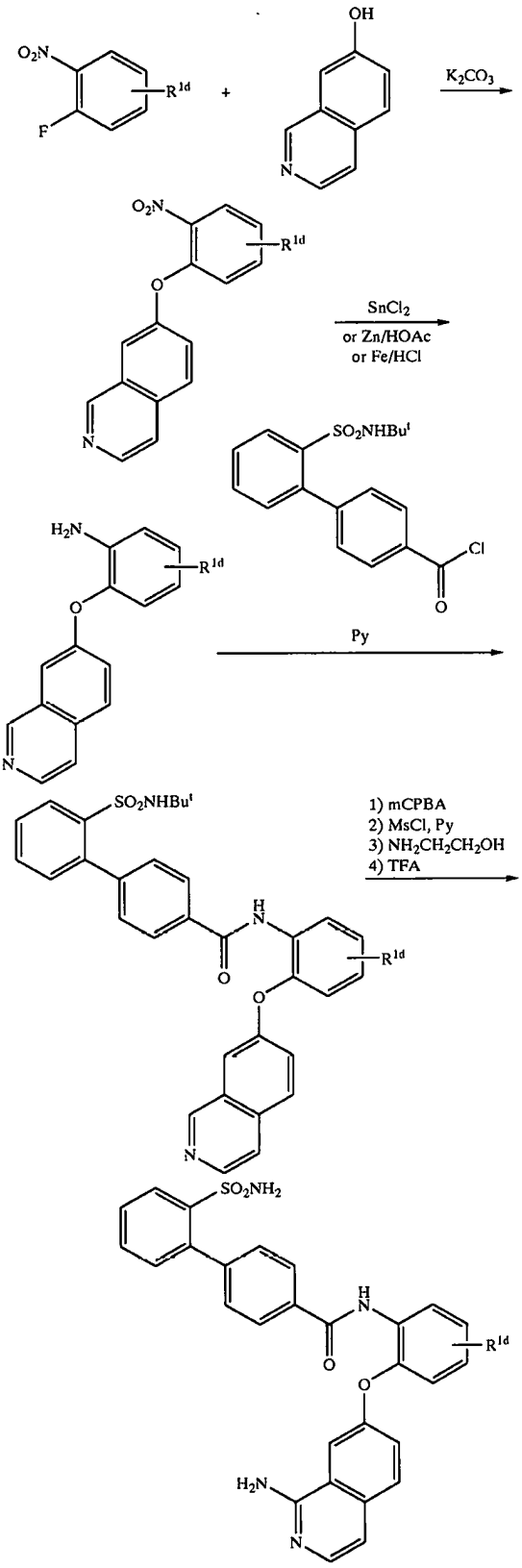
EXAMPLES

Examples of Chemical Production Process General Reaction Schemes

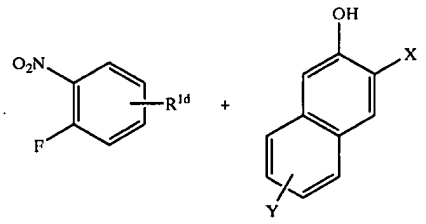
Scheme 1

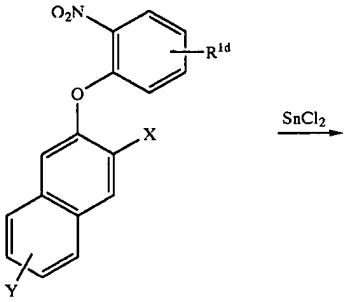


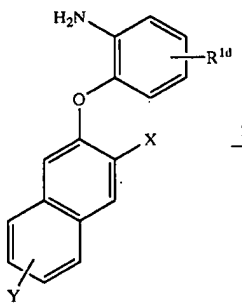
Scheme 2

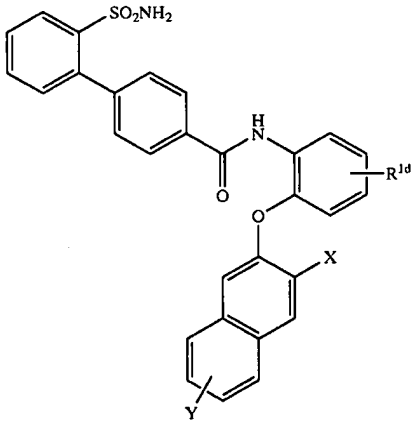


Scheme 3









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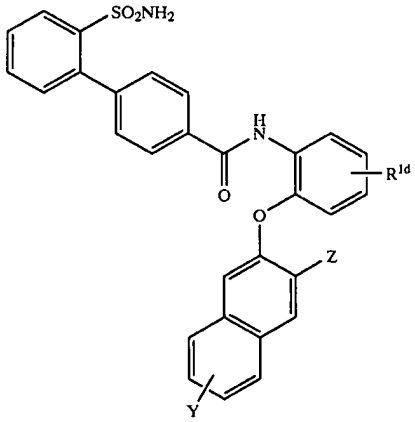
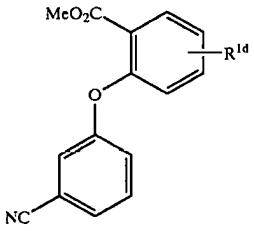
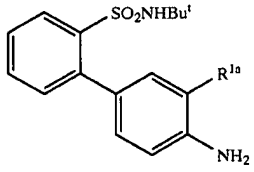
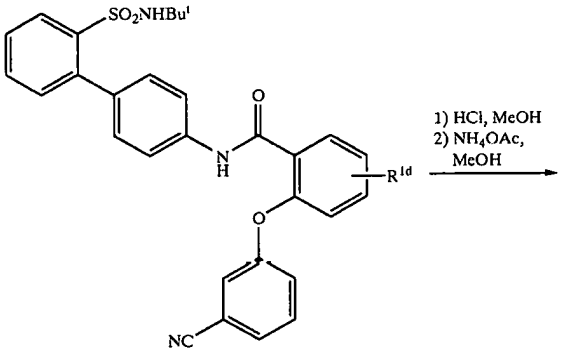
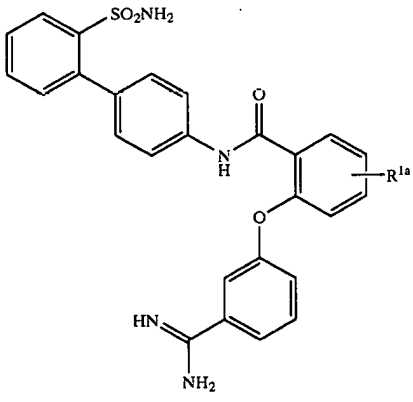


Scheme 4

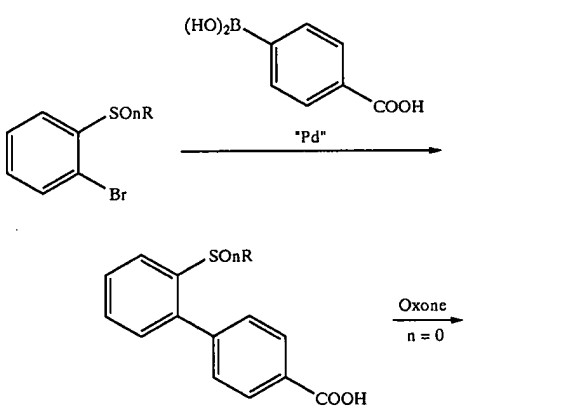




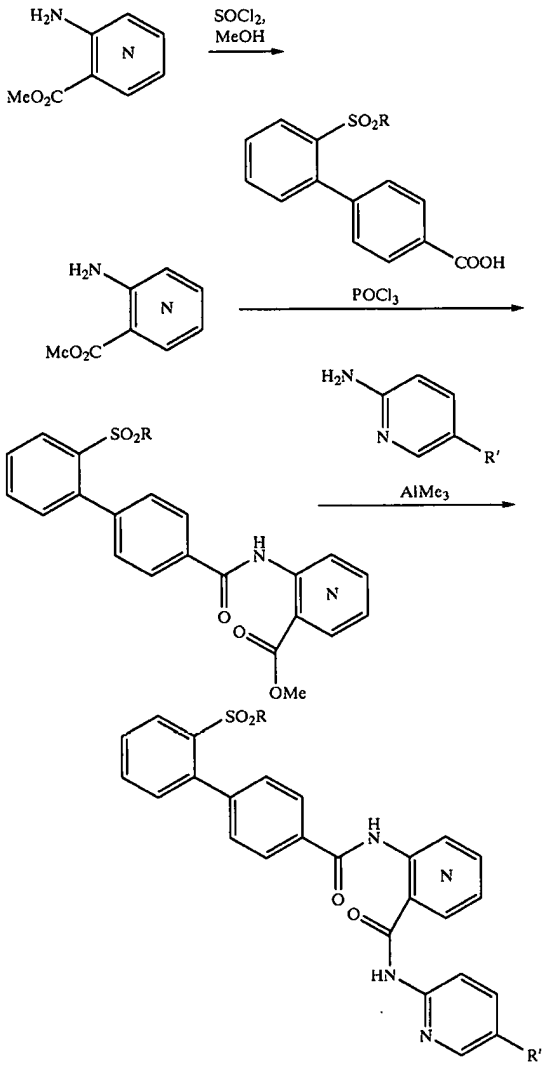




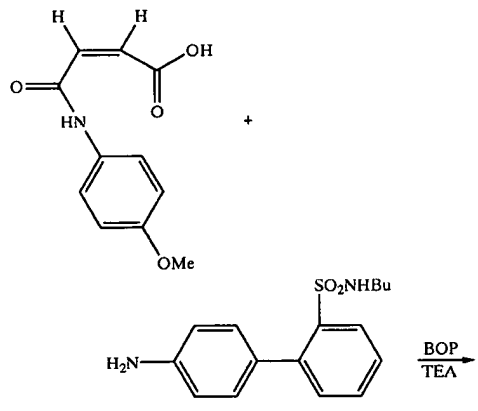
Scheme 5



Scheme 6



Scheme 7



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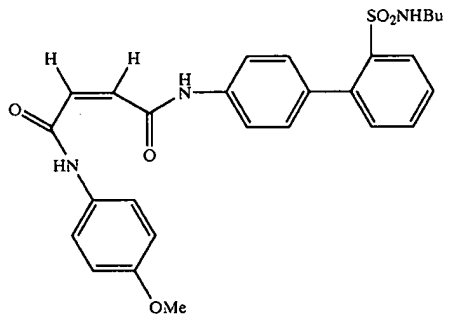

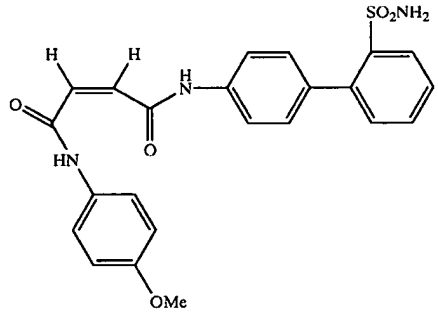

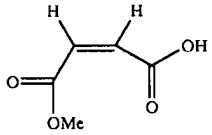

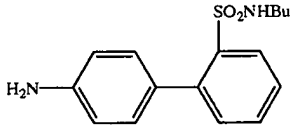

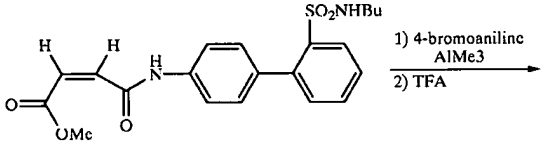

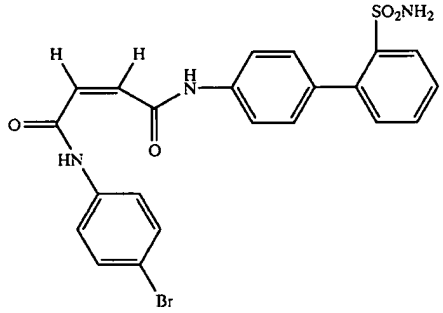

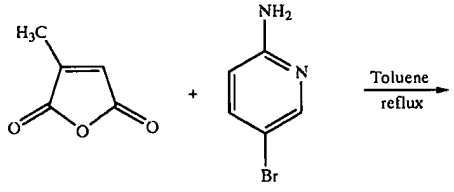

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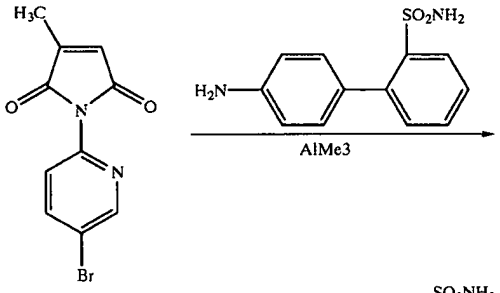
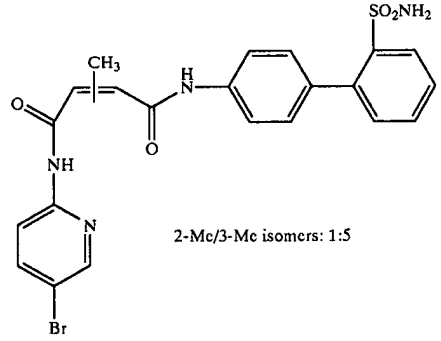
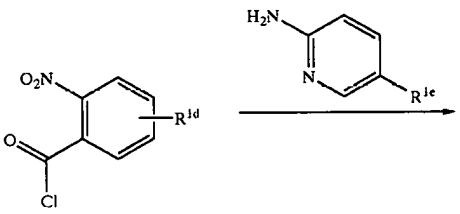
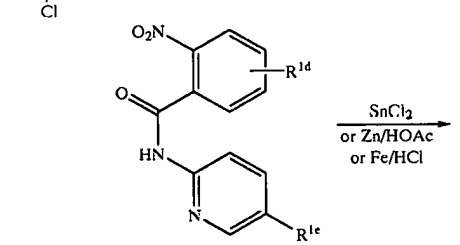


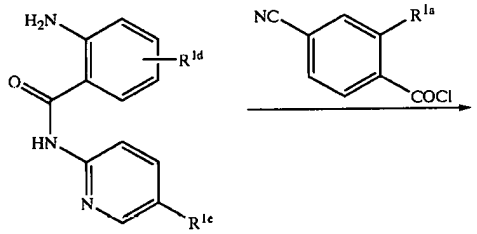


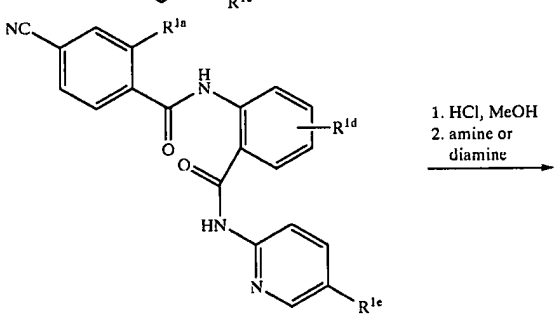
2-Me/3-Me isomers: 1:5

Scheme 8









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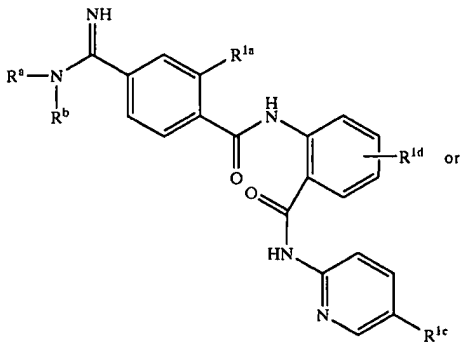

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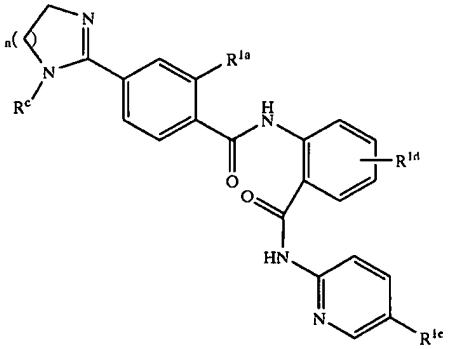
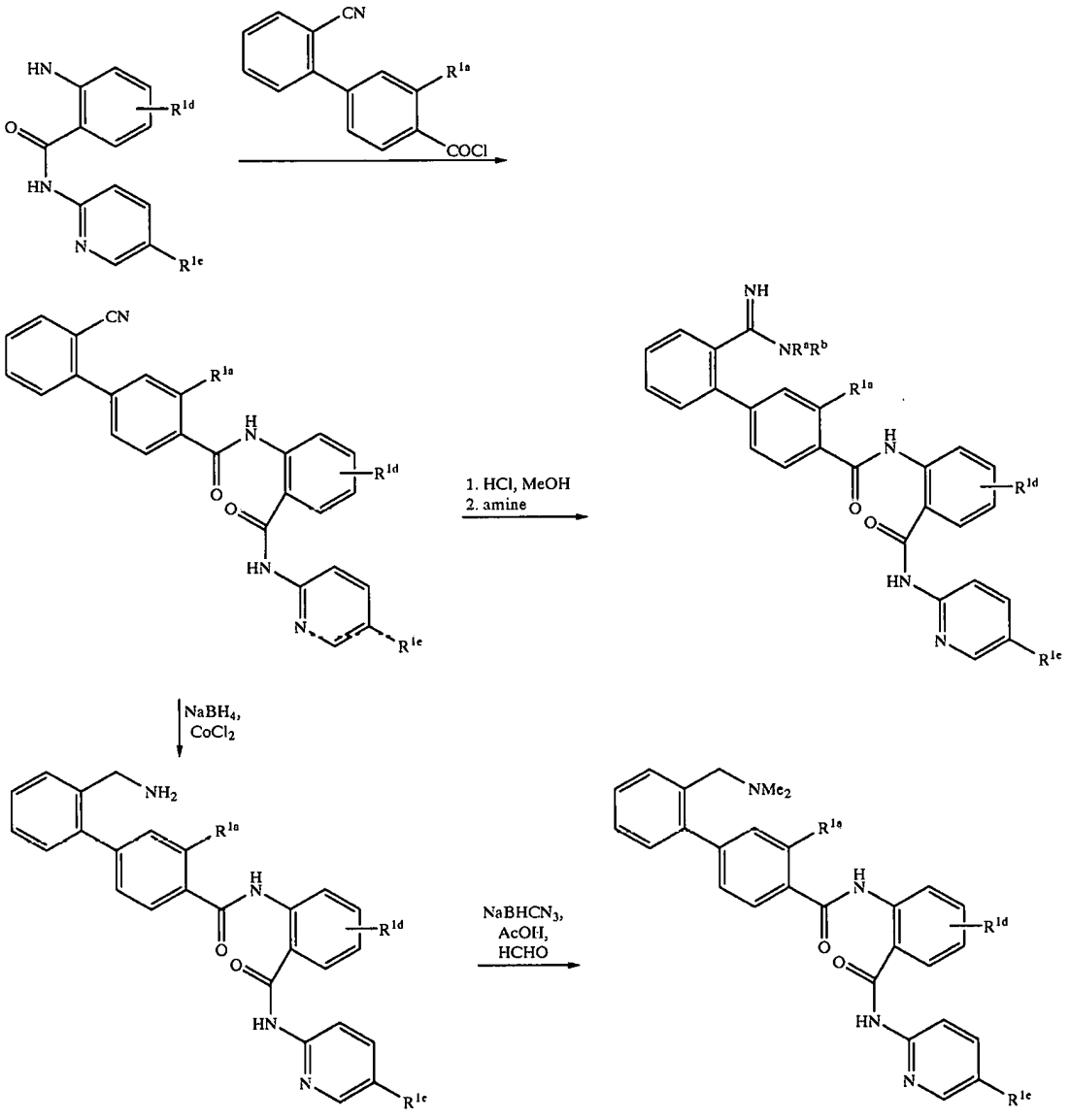
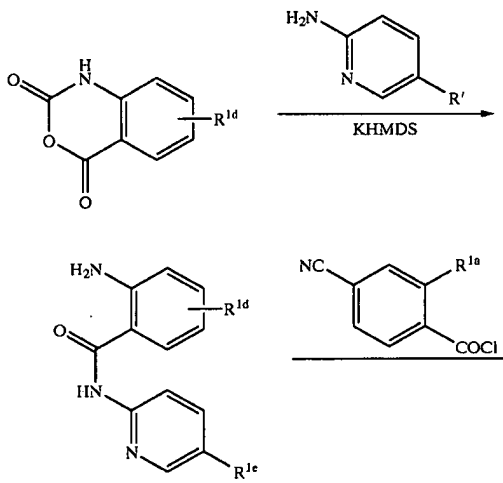


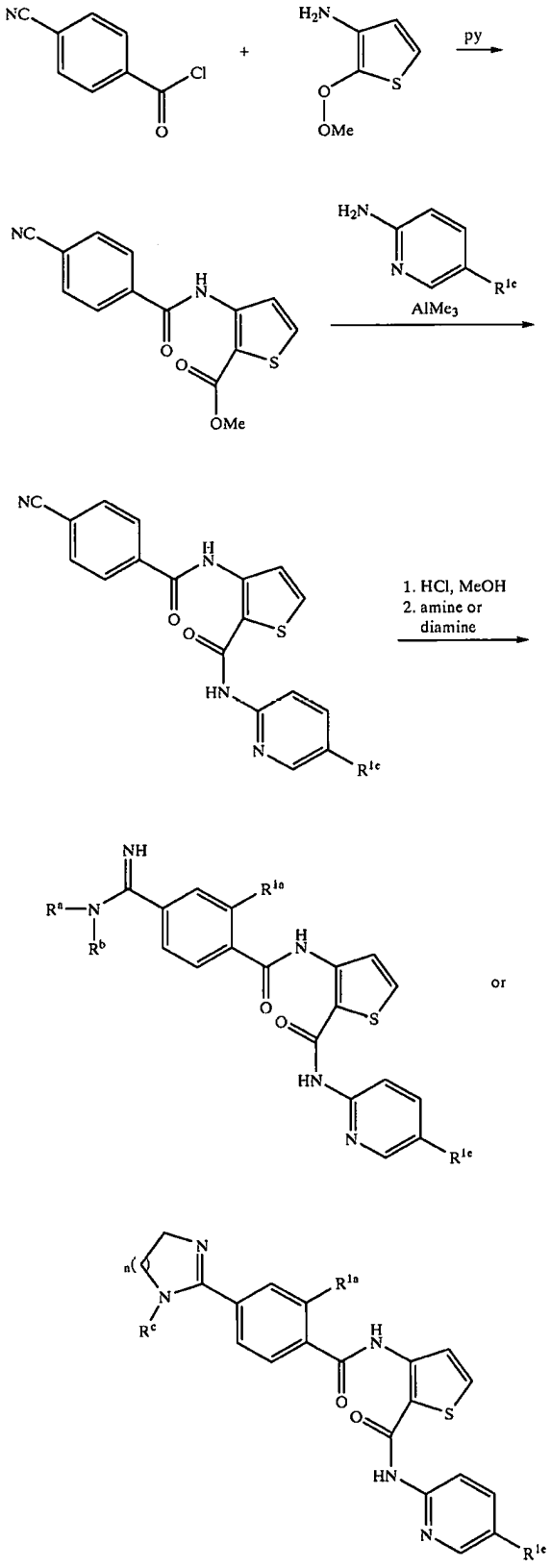
Scheme 9



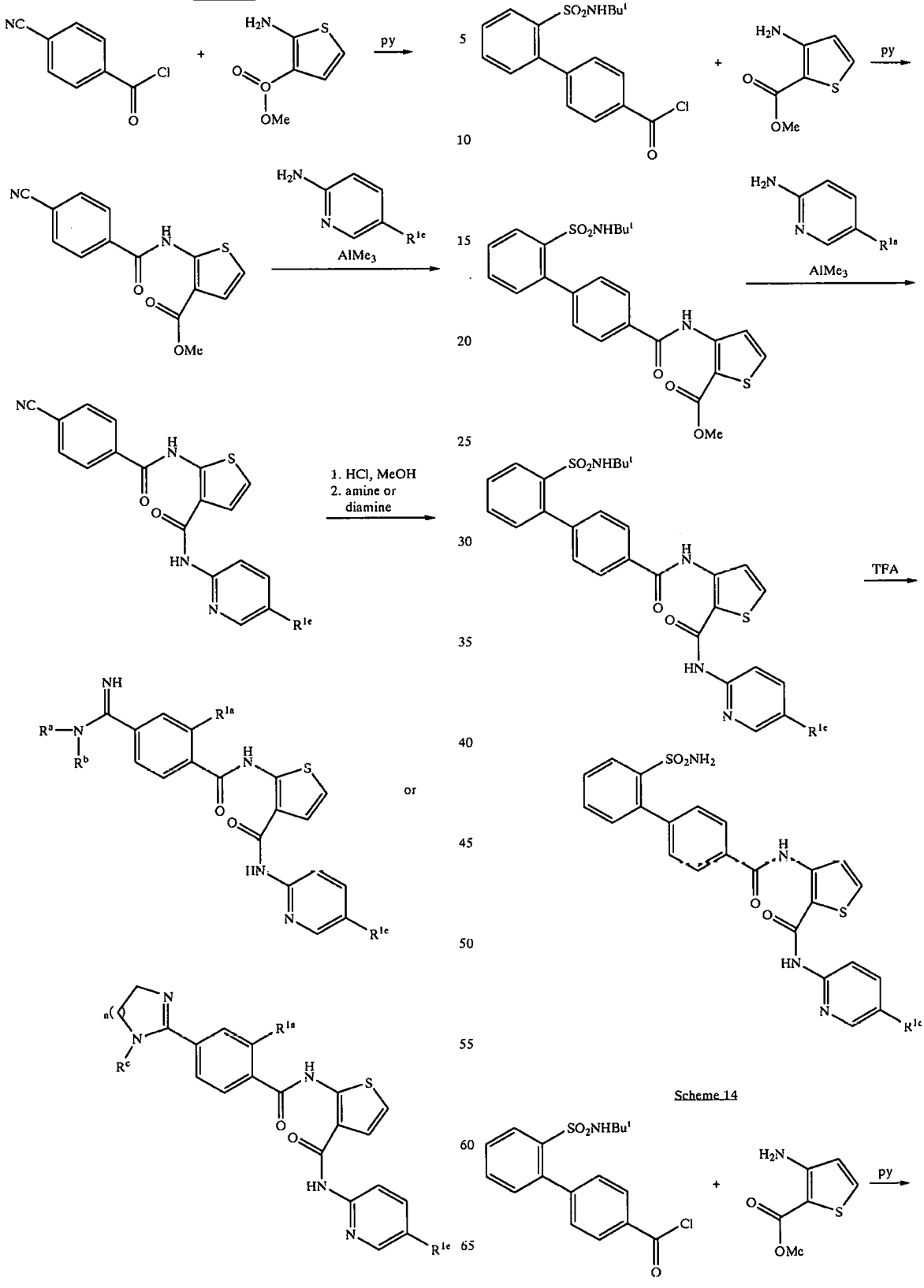
Scheme 10



Scheme 11



Scheme 12



Scheme 13

Scheme 14

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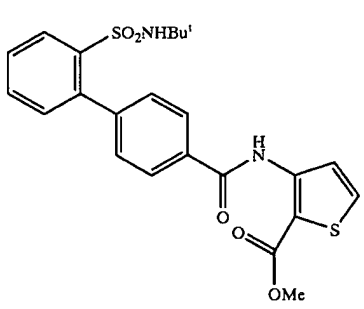

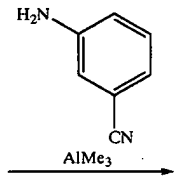

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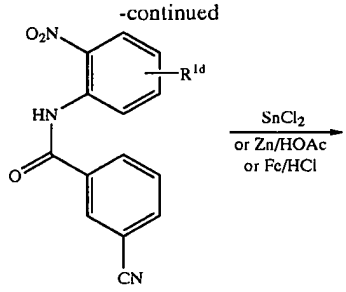
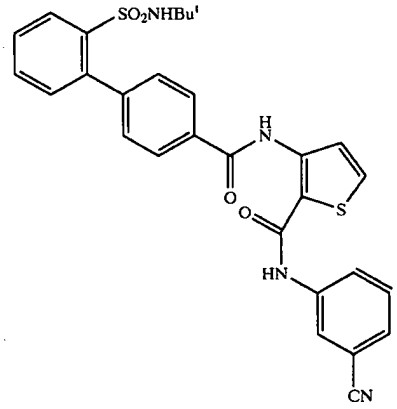
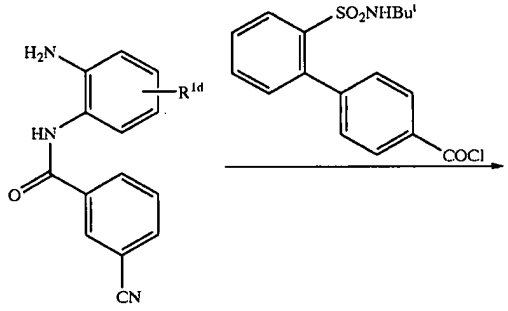
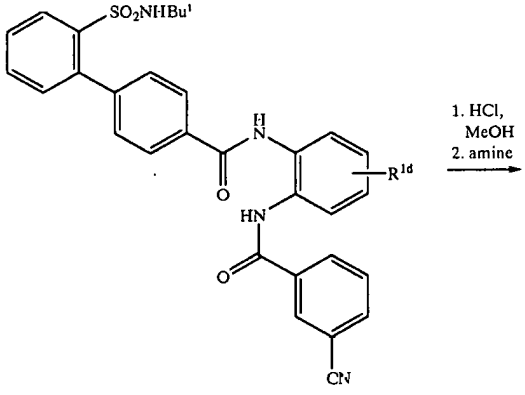
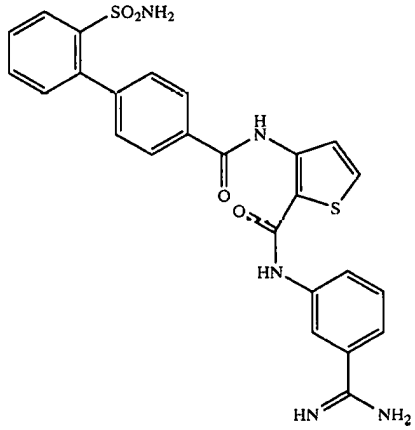
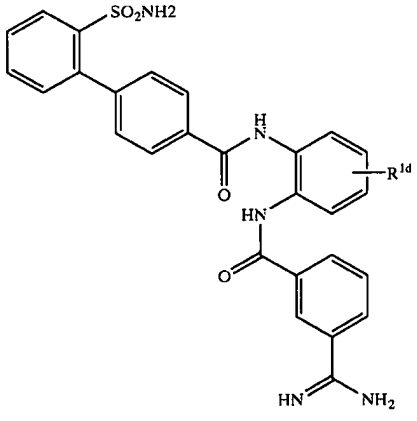




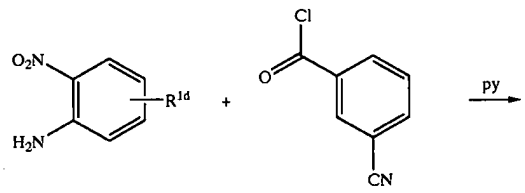




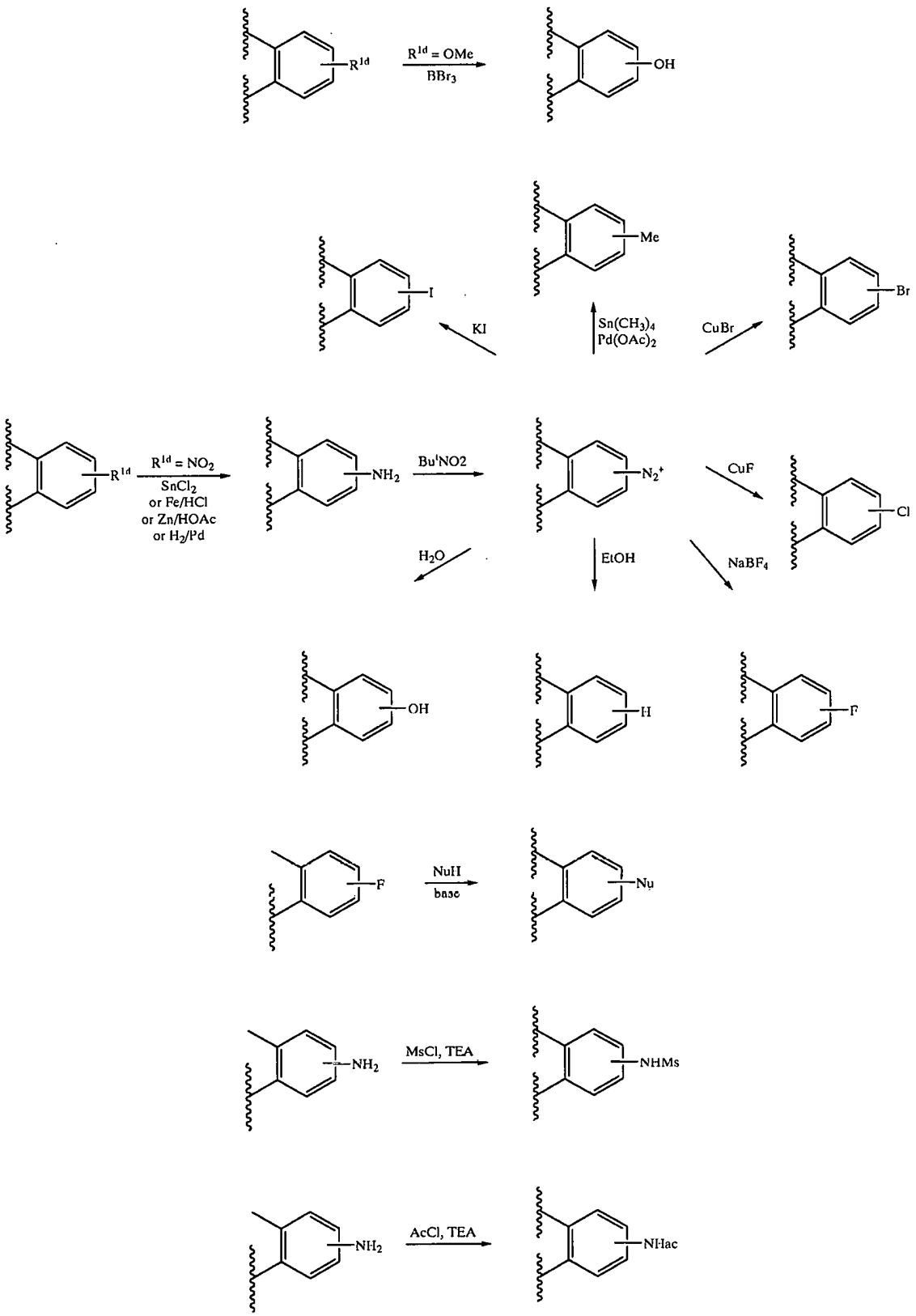




Scheme 15

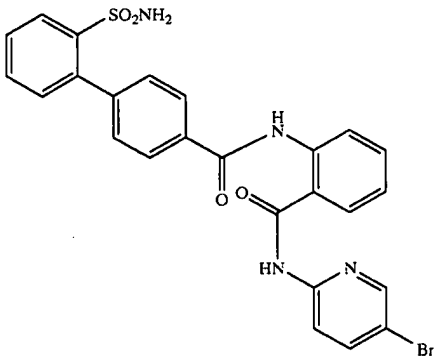


Scheme 16: Transformations of R^{1d}



Example 1

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)phenylcarboxamide



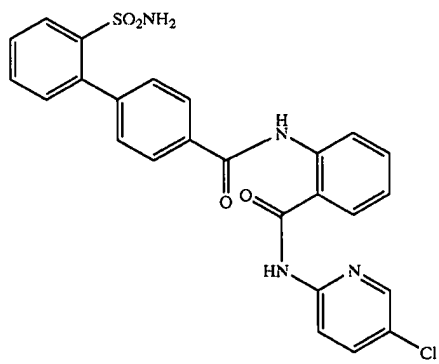
Step 1: A solution of 2-ntrobenzoyl chloride (3.70 g, 20 mmol, 1.0 equiv), 2-amino-5-bromopyridine (3.50 g, 1.0 equiv), pyridine (10 mL) in 25 mL of methylene chloride was stirred overnight. The volatile was evaporated, flash chromatography on silica gel gave N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (5.02 g, 77%). MS found for $C_{12}H_9BrN_3O_3$ $(M+H)^+$: 322.

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro) phenylcarboxamide (1.0 g, 3.1 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with $SnCl_22H_2O$ (2.80 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (0.89 g, 98%). MS found for $C_{12}H_{11}$ BrN_3O $(M+H)^+$: 292.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino) phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenylcarboxamide (470 mg, 85%). MS found for $C_{25}H_{20}BrN_4O_4S$ $(M+H)^+$: 551.

Example 2

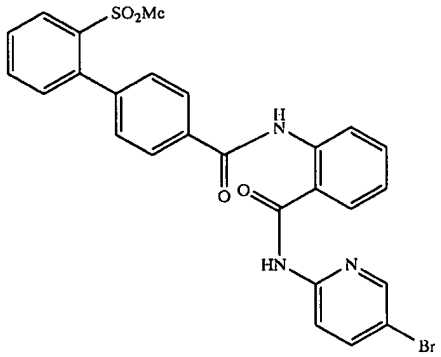
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)phenylcarboxamide



A mixture of N-(5-chloro-2-pyridinyl)-(2-amino) phenylcarboxamide (247 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino) phenylcarboxamide (370 mg, 73%). MS found for $C_{25}H_{20}ClN_4O_4S$ $(M+H)^+$: 507.

Example 3

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl) phenyl]phenylcarbonyl)amino)phenylcarboxamide



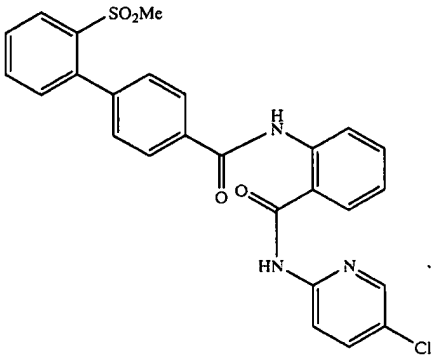
Step 1: To a mixture of 2-bromothioanisole (4.8 g, 23.6 mmol), 4-carboxybenzeneboronic acid (3.92 g, 23.6 mmol) and 2M K_2CO_3 (35.5 mmol, 71 mmol) in dioxane (20 ml) was added dichlorobis(triphenylphosphine) palladium (II) (415 mg, 0.6 mmol) under Ar. It was refluxed for 2 hrs. After the removal of the solvent, the residue was neutralized by 1N HCl and extracted with dichloroethane. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 4-[(2-methylthio) phenyl]benzoic acid (5.9 g, 100%). ES-MS $(M+H)^+$=245.

Step 2: To a solution of 4-[(2-methylthio)phenyl]benzoic acid (3.43 g, 14 mmol) in H_2O (10 ml) and acetone (20 ml) was added oxone monopersulfate (34.6 g, 56 mmol). The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give 2.16 g (63%) 4-[(2-methylsulfonyl)phenyl]benzoic acid. ES-MS $(M+H)^+$= 277.

Step 3: To a solution of 4-[(2-methylsulfonyl)phenyl] benzoic acid (552 mg, 2 mmol) in dichloromethane (5 ml) was added oxalyl chloride (350 ul, 4 mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent in vacuo, the residue was dissolved in dichloromethane (5 ml), N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (700 mg, 2.4 mmol), pyridine (486 ul, 6 mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 41.4 mg (38%) of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino) phenylcarboxamide. ES-MS M^+=550, $(M+2)^+$=552.

Example 4

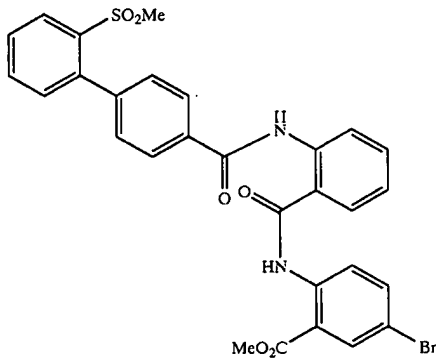
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl) phenyl]phenylcarbonyl)amino)phenylcarboxamide



To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol) in dichloromethane (5 ml) was added oxalyl chloride (175 ul, 2 mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent in vacuo, the residue was dissolved in dichloromethane (5 ml), N-(5-chloro-2-pyridinyl)-(2-amino) phenylcarboxamide (297 mg, 1.2 mmol), pyridine (243 ul, 3 mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 95 mg (20%) of N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino) phenylcarboxamide. ES-MS M+=505.5, (M+2)+=507.5.

Example 5

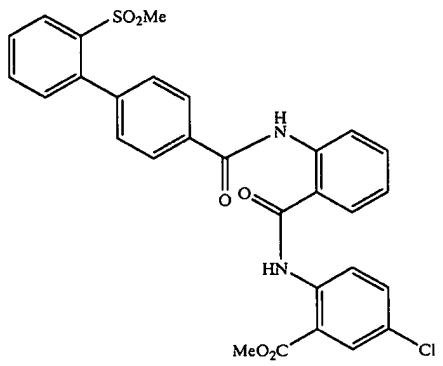
N-(4-bromo-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino) phenylcarboxamide



A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-bromo-2-methoxycarbonyphenyl)-(2-amino)phenylcarboxamide (348 mg, 1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 480 mg (79%) of N-(4-bromo-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino) phenylcarboxamide. MS found for $C_{29}H_{24}BrN_2O_6S$ $(M+H)^+$: 607.

Example 6

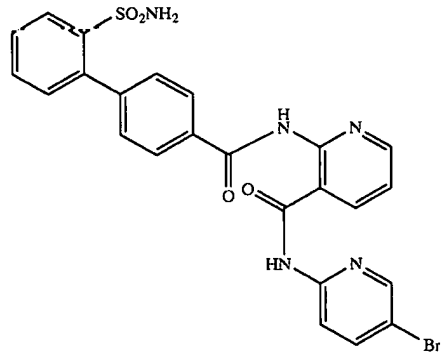
N-(4-chloro-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino) phenylcarboxamide



A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-chloro-2-methoxycarbonyphenyl)-(2-amino)phenylcarboxamide (304 mg, 1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 479 mg (85%) of N-(4-chloro-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino) phenylcarboxamide. MS found for $C_{29}H_{24}ClN_2O_6S$ $(M+H)^+$: 563.

Example 7

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide



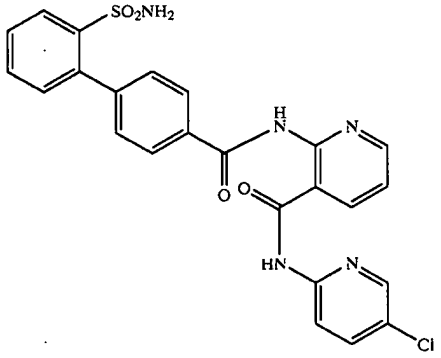
Step 1: A solution of 2-aminopyridine-3-carboxylic acid (138 mg, 1 mmol) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid and $POCl_3$. The

resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographed to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (243 mg, 52%). MS found for $C_{24}H_{26}N_3O_5S$ $(M+H)^+$: 468.

Step 2: To A solution of 2-amino-5-bromopridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/ CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (17 mg, 48%). MS found for $C_{24}H_{19}BrN_5O_4S$ $(M+H)^+$: 552.

Example 8

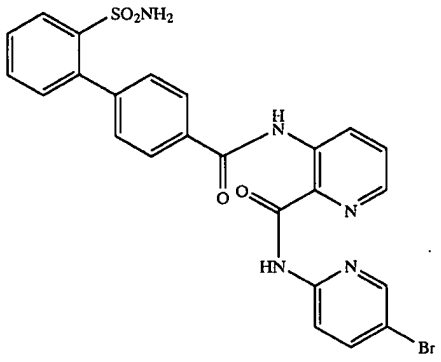
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide



To A solution of 2-amino-5-chloropridine (32 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl) aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (21 mg, 66%). MS found for $C_{24}H_{19}ClN_5O_4S$ $(M+H)^+$: 508.

Example 9

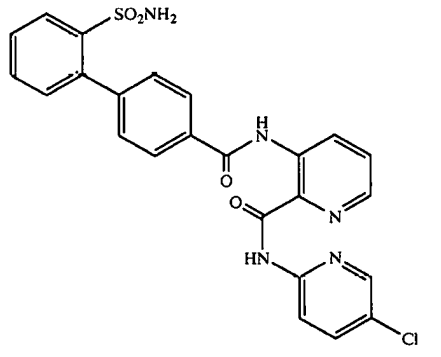
N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide



To A solution of 2-amino-5-bromopridine (69.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl) aminopyridine-2-carboxylate (46.7 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide (29 mg, 53%). MS found for $C_{24}H_{19}BrN_5O_4S$ $(M+H)^+$: 552.

Example 10

N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide



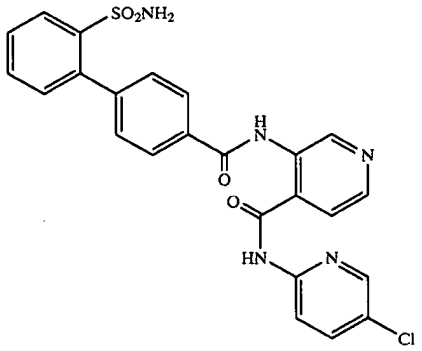
To A solution of 2-amino-5-chloropridine (51.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl) aminopyridine-2-carboxylate (46.7 mg, 0.1 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and

refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonyl-amino)pyridinyl-3-carboxamide (33 mg, 64%). MS found for $C_{24}H_{19}ClN_5O_4S$ $(M+H)^+$: 508.

Examples 11–14

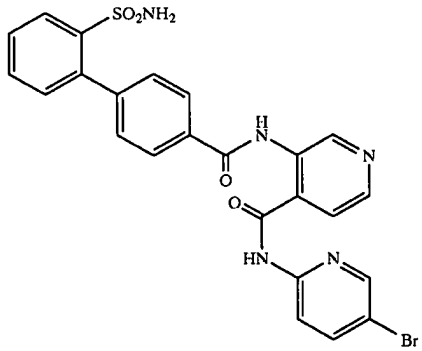
The following compounds were prepared using the procedure described previously:

Example 11



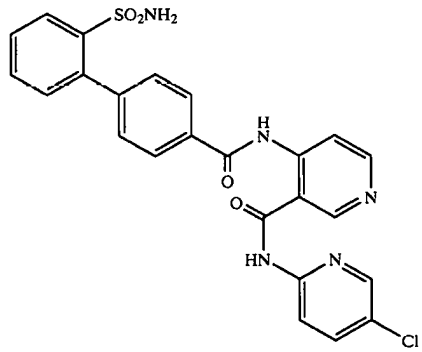
MS (M+H):508

Example 12



MS (M+H):552

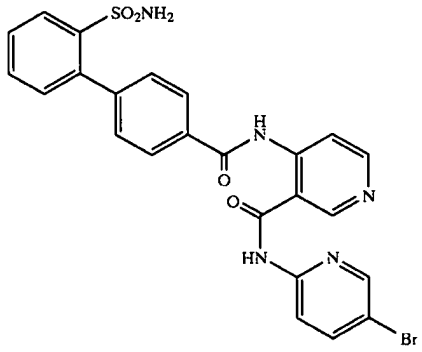
Example 13



MS (M+H):508

-continued

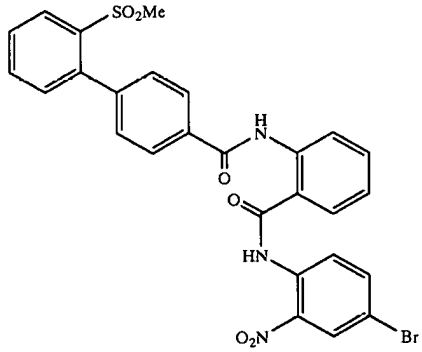
Example 14



MS (M+H):552

Example 15

N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino) phenylcarboxamide

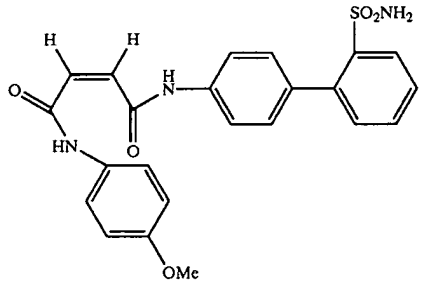


Step 1: A mixture of methyl 2-aminobenzoate (150 mg, 1 mmol, 1.0 equiv), 4-[(2-methylsulfonyl)phenyl]benzoic chloride (294 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl) aminobenzoate (250 mg, 54%). MS found for $C_{25}H_{27}N_2O_5S$ $(M+H)^+$: 467.

Step 2: To a solution of 4-bromo-2-ntroaniline (43.4 mg, 0.2 mmol, 2.0 equiv) in 5 ml, of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.3 mL, 6 equiv) for 30 min was added methyl 2-(4-[(2-methylsulfonyl)phenyl] phenylcarbonyl)aminobenzoate (46.6 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl] phenylcarbonyl)amino)phenylcarboxamide (5 mg, 9%). MS found for $C_{27}H_{21}BrN_3O_6S$ $(M+H)^+$: 594.

Example 16

N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl) phenyl]phenyl)-maleamic amide



A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide.

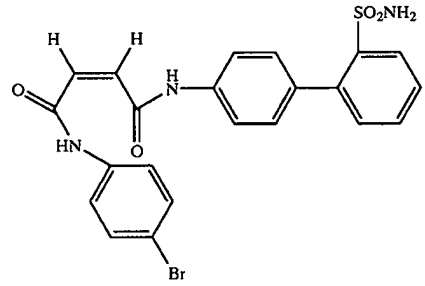
To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL), BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H2O, then with 5% NaHCO3, dried over Na2SO4, concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH3CN in H2O (containing 0.1% TFA) to 100% CH3CN over 80 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (70 mg, yield: 31%). MS 508 (M+H).

B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide (40 mg, 79 mol) was dissolved in TFA (3 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H_2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M+H) and 474 (M+Na). ^{1}H NMR (CDCl3) δ 11.40 (br.s, 1H), 10.28 (br.s, 1H), 8.12 (d, 1H, J=8 Hz), 7.72 (d, 2H, J=8 Hz), 7.60–7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 17

N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl] phenyl)-maleamic amide



A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester.

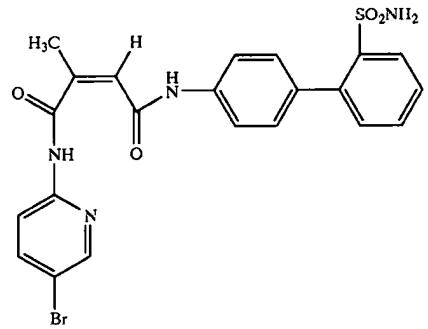
To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonylphenyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH2Cl2 (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH2Cl2 solution was then washed with sat. NaHCO3, 1N HCl and sat. NaCl. The solution was dried over Na2SO4, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10–40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M+H–^{t}Bu) and 439 (M+Na).

B. Preparation of N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH2Cl2 (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound N-(4-[(2-tert-butylaminosulfonyl) phenyl]phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2-3. Water and CH2Cl2 were added, and organic phase was separated, dried over Na2SO4, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M+H), 522 and 524 (M+Na). ^{1}H NMR (CD3OD) δ 8.09 (d, 1H, J=8 Hz), 7.68 (d, 2H, J=8 Hz), 7.64–7.28(m, 9H), 6.45 (AB type, 2H).

Examples 18 and 19

Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide



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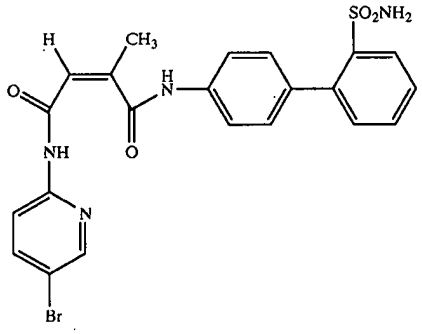


A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

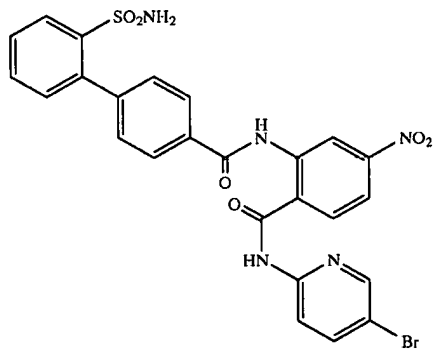
A mixture of citraconic anhydride (1.00 mL, 11.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight. The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 (M+H).

B. Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl) phenyl]phenyl)-3-methylmaleamic amide.

To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH2Cl2 (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH2Cl2 (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2–3, which resulted in precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1:5. MS 515 and 517 (M+H), 537 and 539 (M+Na).

Example 20

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide



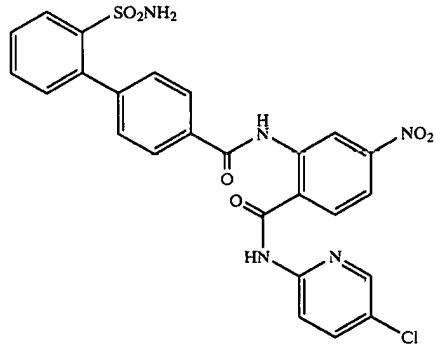
Step 1: A solution of 2-amino-4-nitrobenzoic acid (182 mg, 1 mmol, 1 equiv) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv) and $POCl_3$ (0.93 mL, 10 equiv). The resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (430 mg, 84%). MS found for $C_{25}H_{26}N_3O_7S$ $(M+H)^+$: 512.

Step 2: To A solution of 2-amino-5-bromopridine (135 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 10 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonyl)amino-4-nitrobenzoate (100 mg, 0.2 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide (42 mg, 36%). MS found for $C_{25}H_{19}BrN_5O_6S$ $(M+H)^+$: 596.

Examples 21–23

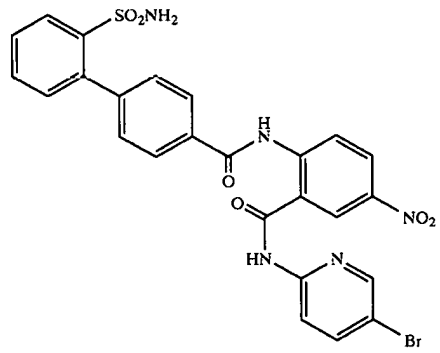
The following compounds were prepared according to the procedure described previously:

Example 21



MS (M+H):552

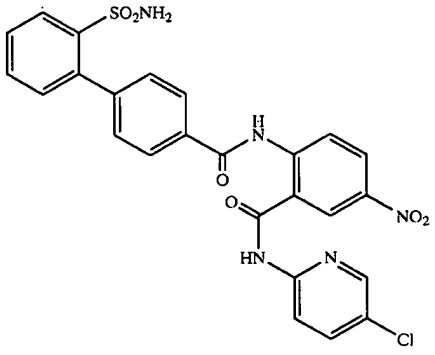
Example 22



MS (M+H):596

-continued

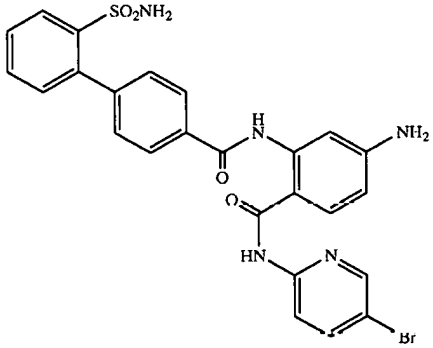
Example 23



MS (M+H):552

Example 24

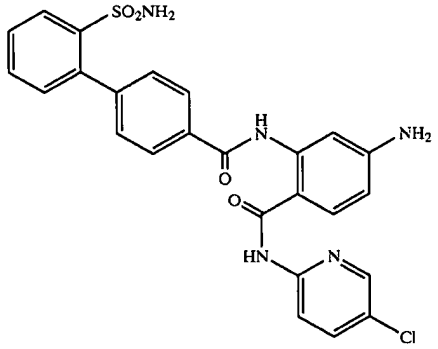
N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide



A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-nitrophenylcarboxamide (65 mg, 0.1 mmol, 1 equiv) in 10 mL of EtOAc was treated with $SnCl_2 2H_2O$ (90 mg, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl] phenylcarbonyl) amino)-4-aminophenyl carboxamide, which was refluxed with 2 mL of TFA for 1 h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide (47 mg, 84%). MS found for $C_{25}H_{21}BrN_5O_4S$ $(M+H)^+$: 566.

Example 25

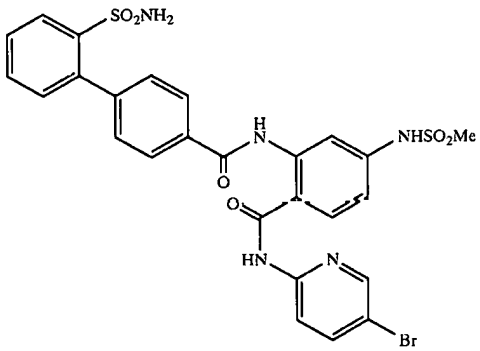
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide



This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}ClN_5O_4S$ $(M+H)^+$: 522.

Example 26

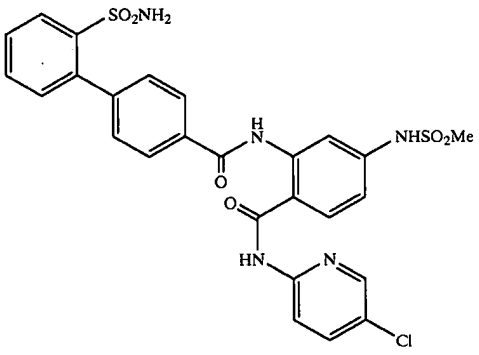
N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide



A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide (62 mg, 0.1 mmol, 1 equiv) in 3 mL of CH_2Cl_2 was treated with MsCl (23 mg, 2 equiv) and TEA (0.5 mL) at rt for 4 h. The mixture was washed with water and dried over $MgSO_4$, filtered and evaporated. The residue was refluxed with 2 mL of TFA for 1 h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-[2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide (33 mg, 52%). MS found for $C_{26}H_{23}BrN_5O_6S2$ $(M+H)^+$: 644.

Example 27

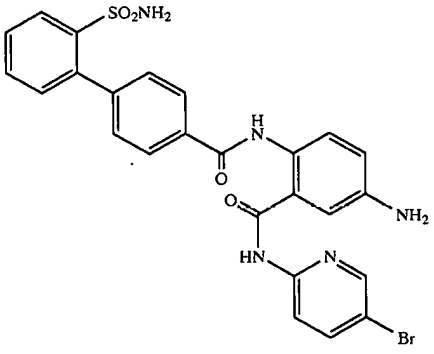
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide



This compound was prepared according to the procedure described in example 53. MS found for $C_{26}H_{23}ClN_5O_6S_2$ $(M+H)^+$: 600.

Example 28

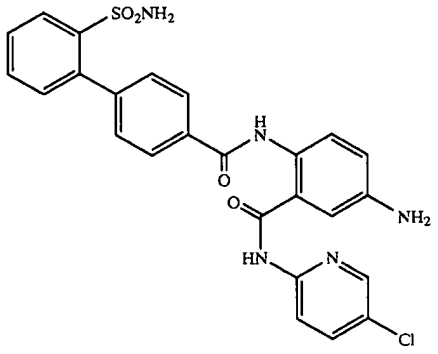
N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide



This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}BrN_5O_4S$ $(M+H)^+$: 566.

Example 29

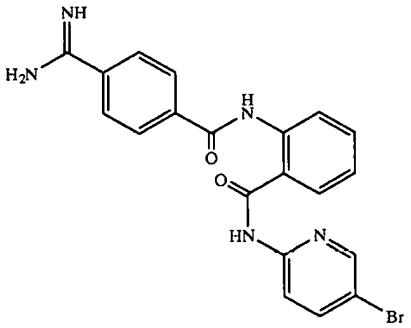
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide



This compound was prepared according to the procedure described in example 50. MS found for $C_{25}H_{21}ClN_5O_4S$ $(M+H)^+$: 522.

Example 30

N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide



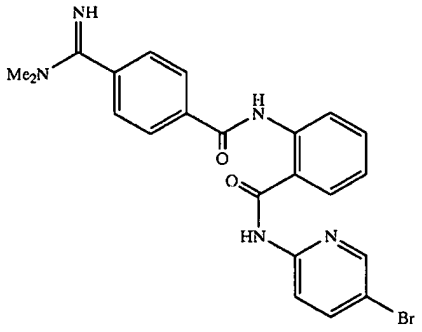
Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino) phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-cyano benzoyl chloride (165 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (349 mg, 70%). MS found for $C_{20}H_{14}BrN_4O_2$ $(M+H)^+$: 421.

Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl) amino)-phenylcarboxamide (31 mg, 70%). MS found for $C_{20}H_{17}BrN_5O_2$ $(M+H)^+$: 438.

Examples 31–60

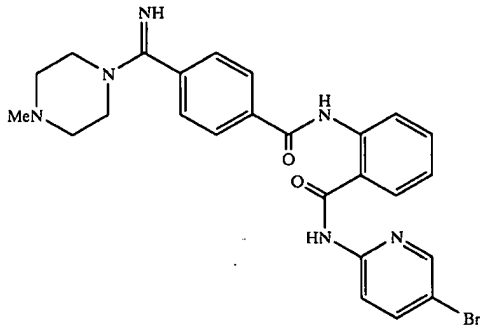
The following compounds were prepared according to the procedure described previously

Example 31



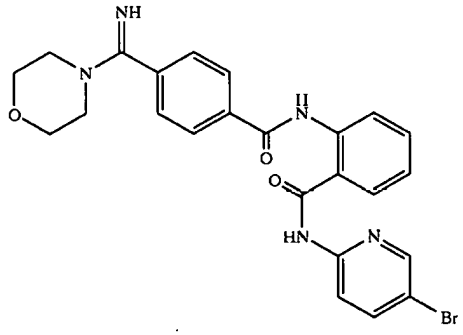
MS (M+H):466

Example 32



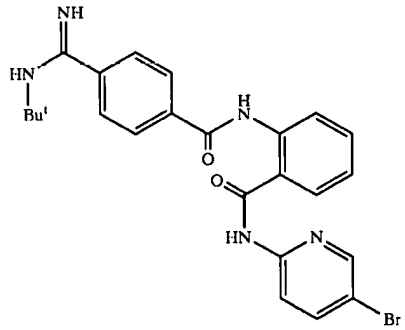
MS (M+H):521

Example 33



MS (M+H):508

Example 34



MS (M+H):494

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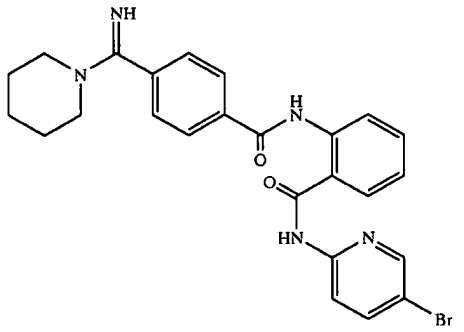
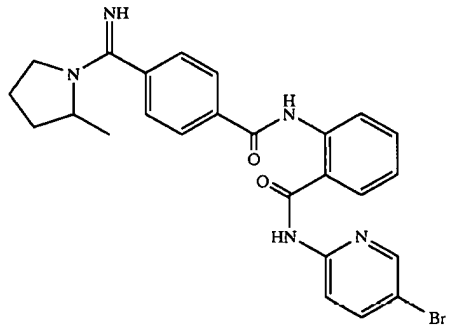
Example 35



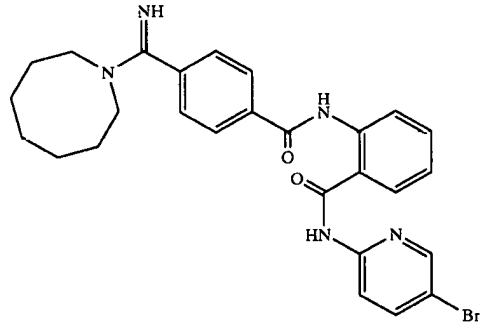
MS (M+H):506

Example 36



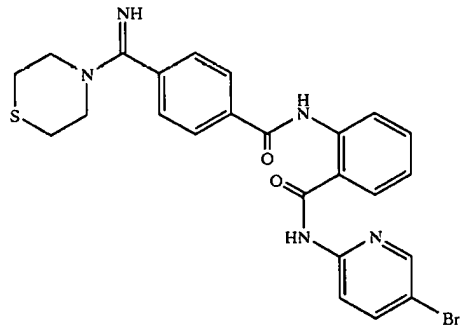
MS (M+H):506

Example 37



MS (M+H):520

Example 38



MS (M+H):524

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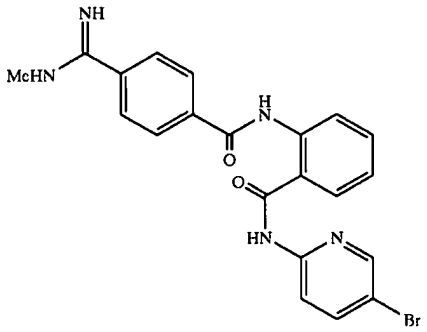
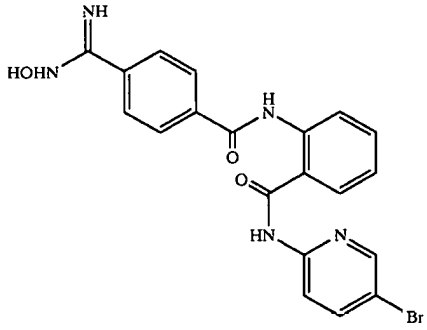
Example 39



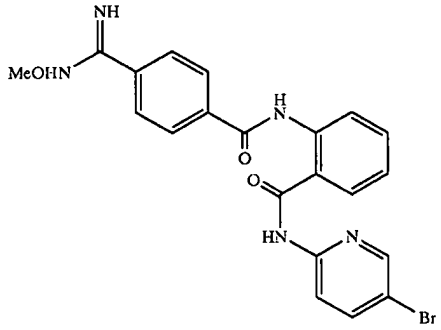
MS (M+H):452

Example 40



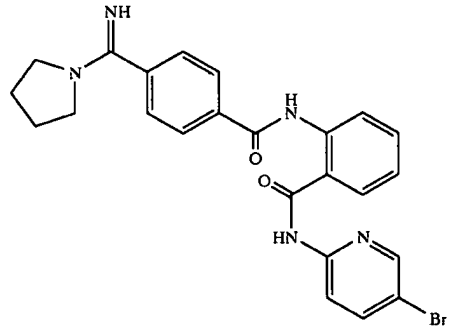
MS (M+H):454

Example 41



MS (M+H):468

Example 42



MS (M+H):492

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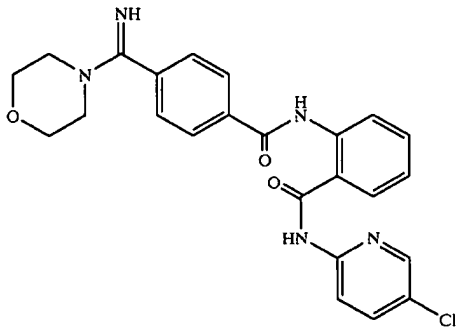
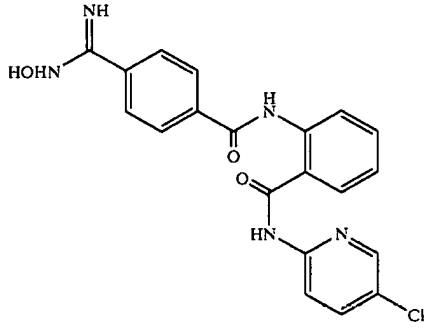
Example 43



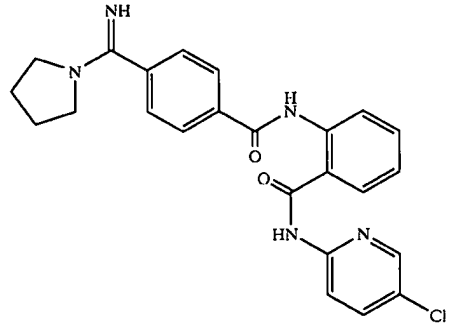
MS (M+H):464

Example 44



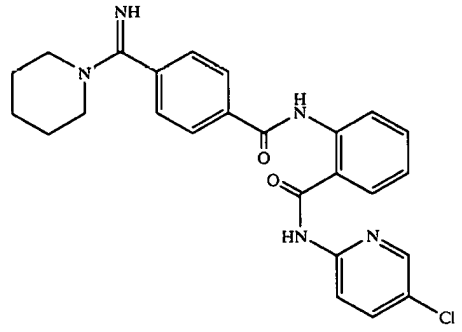
MS (M+H):410

Example 45



MS (M+H):448

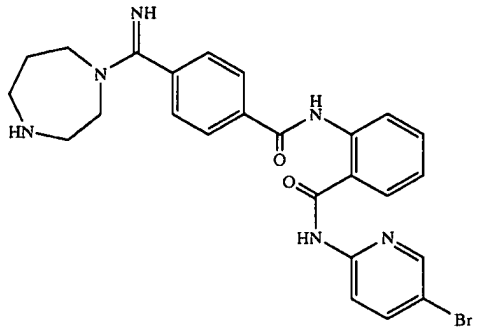
Example 46



MS (M+H):462

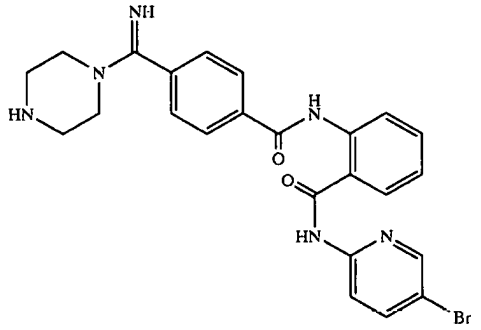
-continued

Example 47



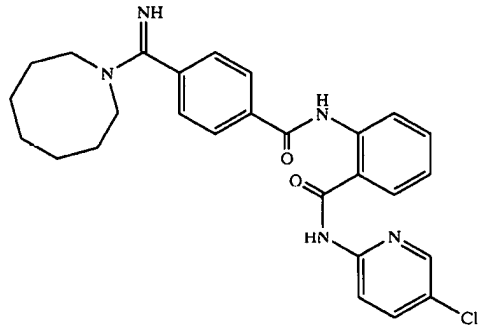
MS (M+H):521

Example 48



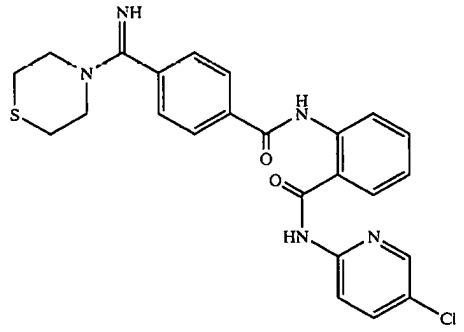
MS (M+H):507

Example 49



MS (M+H):476

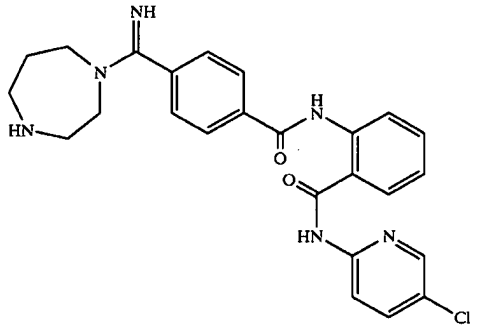
Example 50



MS (M+H):480

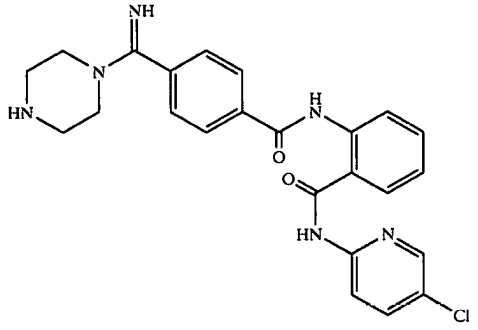
-continued

Example 51



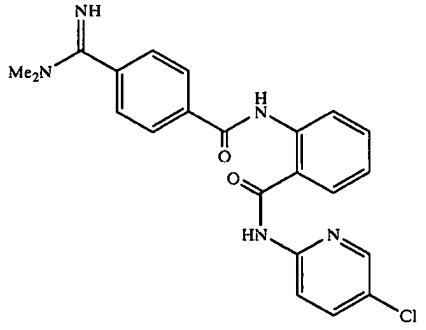
MS (M+H):477

Example 52



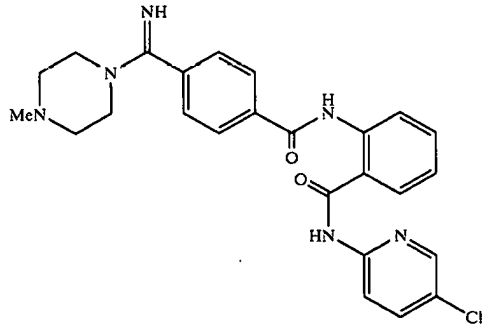
MS (M+H):463

Example 53



MS (M+H):422

Example 54



MS (M+H):477

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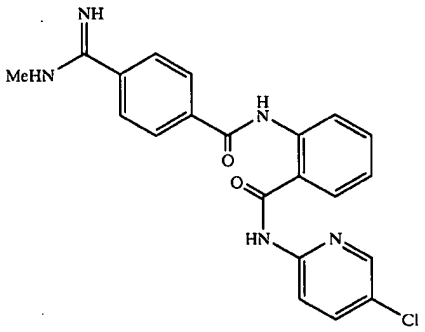
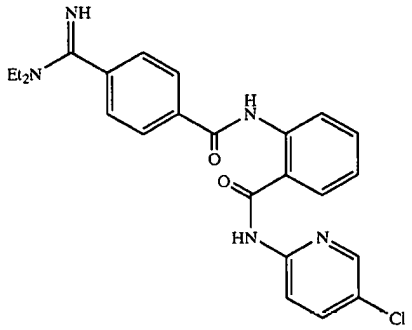
Example 55



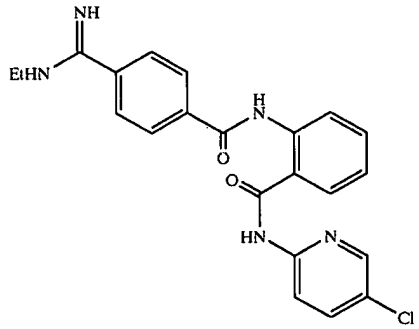
MS (M+H):408

Example 56



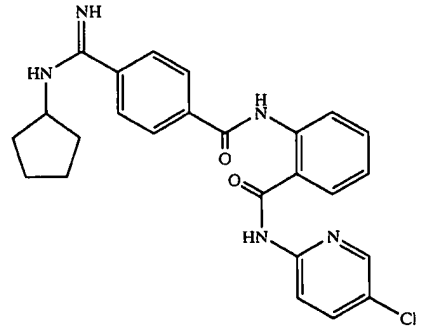
MS (M+H):22

Example 57



MS (M+H):450

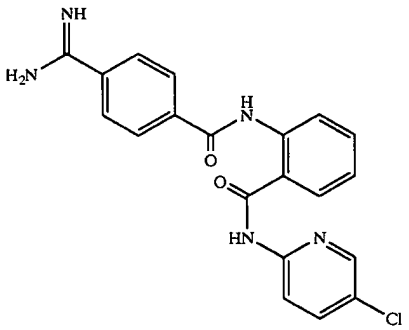
Example 58



MS (M+H):462

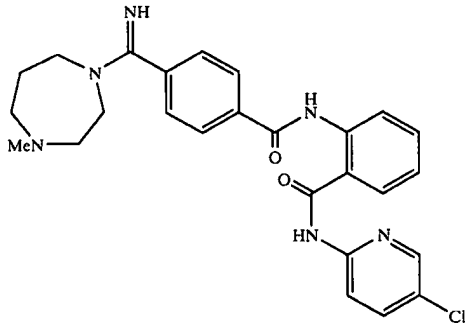
-continued

Example 59



MS (M+H):394

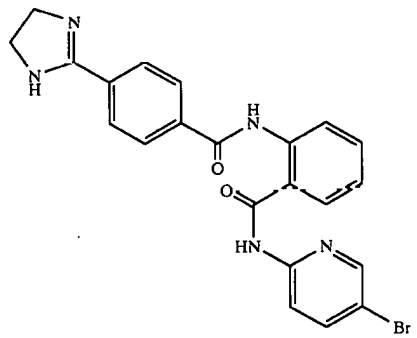
Example 60



MS (M+H):491

Example 61

N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl) phenylcarbonyl)amino)-phenylcarboxamide

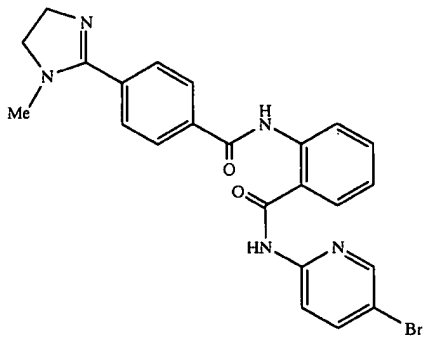


A stream of HCl(g) was bubbled through a 0° C. solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl) amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ethylene diamine (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide (41 mg, 89%). MS found for $C_{22}H_{19}BrN_5O_2$ $(M+H)^+$: 464.

Examples 62-70

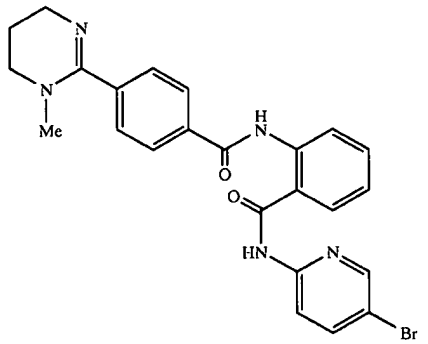
The following compounds were prepared according to the procedure previously described

Example 62



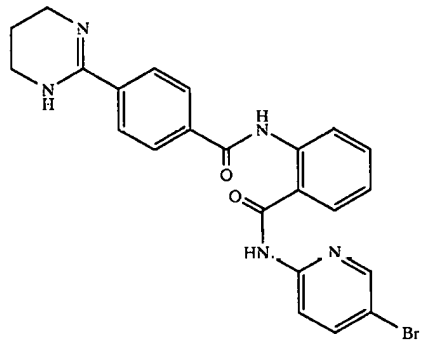
MS (M+H):478

Example 63



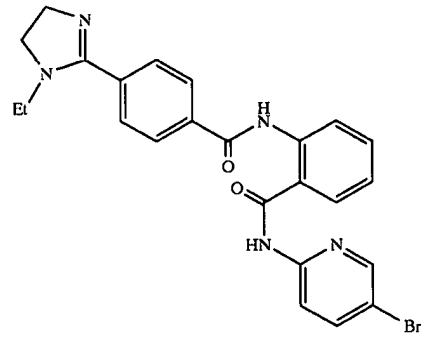
MS (M+H):492

Example 64



MS (M+H):478

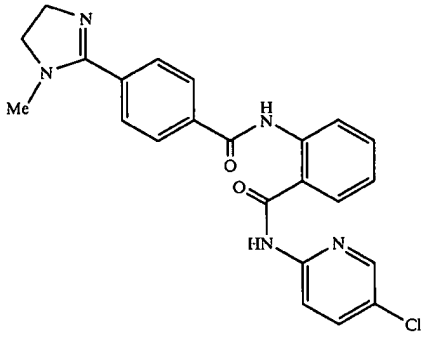
Example 65



MS (M+H):492

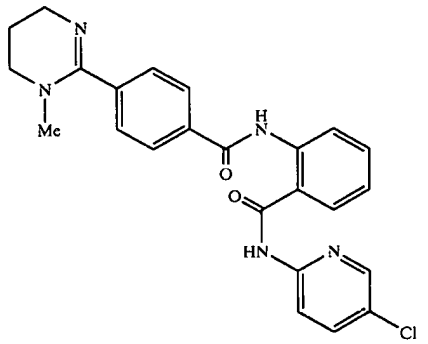
-continued

Example 66



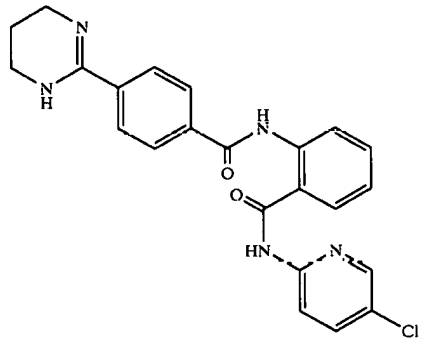
MS (M+H):434

Example 67



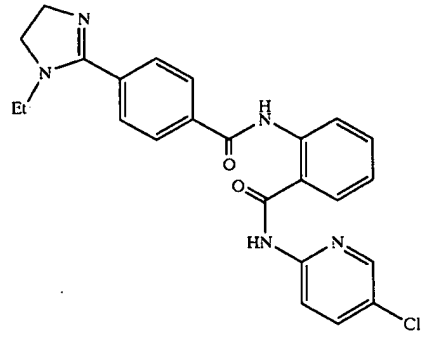
MS (M+H):448

Example 68



MS (M+H):434

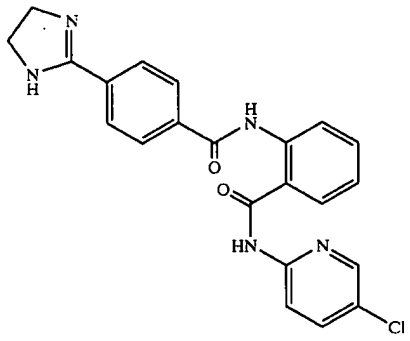
Example 69



MS (M+H):448

-continued

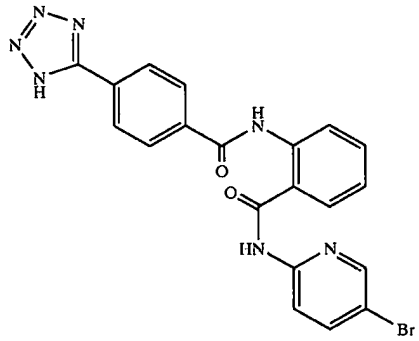
Example 70



MS (M+H):420

Example 71

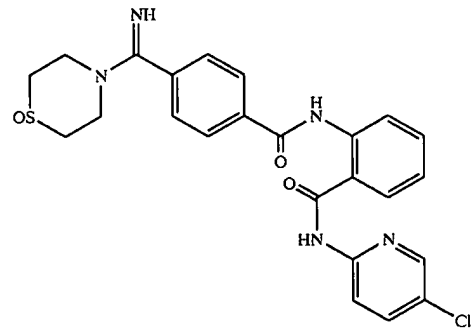
N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl) phenylcarbonyl)amino)-phenylcarboxamide



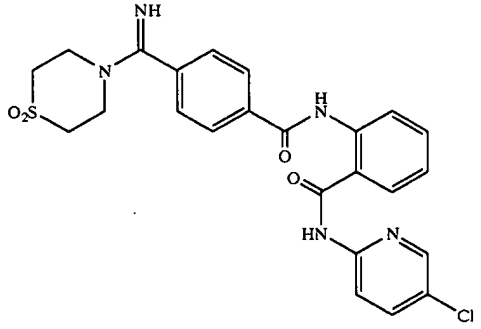
A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenyl-carbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) and sodium azide (67 mg, 10 equiv) in 5 mL of DMF was heated at 100° C. for 24 h. The reaction mixture was diluted with EtOAc, washed with water, dried, filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide (33 mg, 65%). MS found for $C_{20}H_{15}BrN_7O_2$ $(M+H)^+$: 464.

Example 72 and Example 73

N-(5-bromo-2-pyridinyl)-(2-(4[-[1,1-doxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl) amino)-phenylcarboxamide and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl)) iminimethy]phenylcarbonyl)amino)-phenylcarboxamide



-continued

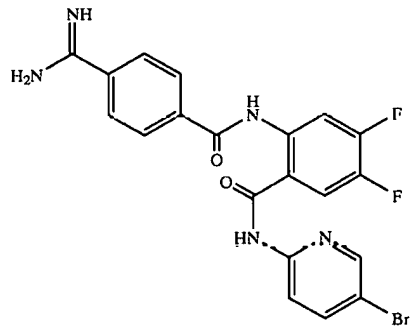


A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-(1,4-thiazaperhydroin-4-yl)iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (48 mg, 0.1 mmol) and and 3 mL of 30% hydrogen dioxide was stirred at rt for 12 h. The reaction was quenched with solid $Na_2S_2O_3$. Purification by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-(4[-[1,1-doxo(1,4-thiazaperhydroin-4-yl))iminimethy]phenylcarbonyl) amino)-phenylcarboxamide (15 mg, 31%), MS found for $C_{24}H_{23}ClN_5O_4S$ $(M+H)^+$: 512 and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl)) iminimethy]phenylcarbonyl)amino)-phenylcarboxamide (20 mg, 41%). MS found for $C_{24}H_{23}ClN_5O_3S$ $(M+H)^+$: 496.

Examples 74–79

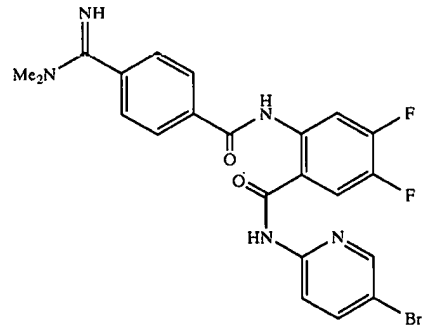
The following compounds were prepared according to the procedure previously described

Example 74



MS (M+H):474

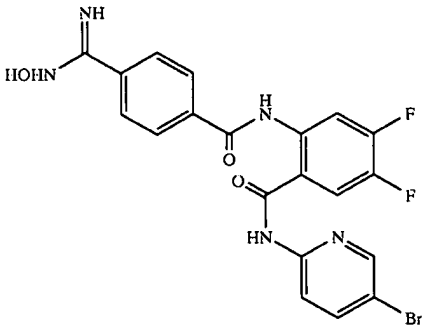
Example 75



MS (M+H):502

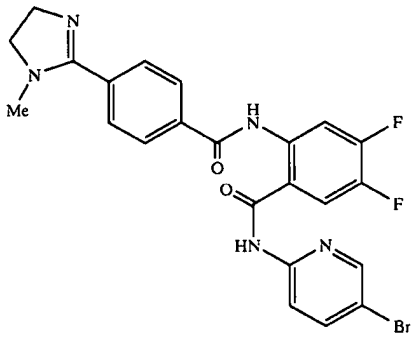
-continued

Example 76



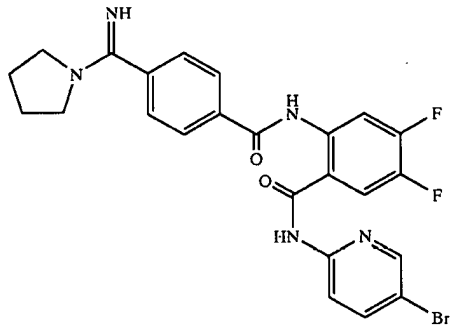
MS (M+H):490

Example 77



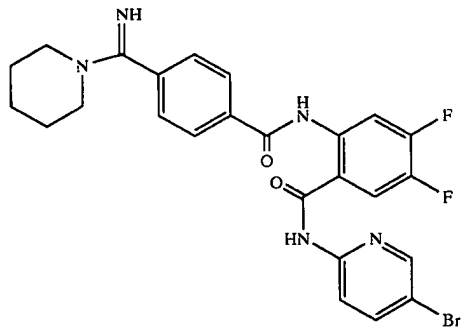
MS (M + H).514

Example 78



MS (M+H):528

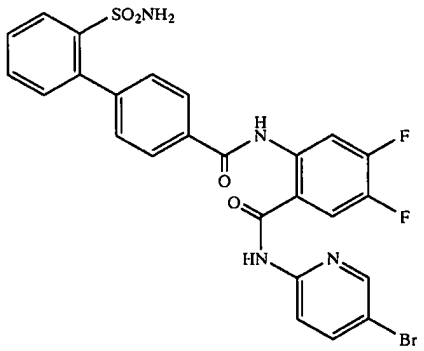
Example 79



MS (M+H):542

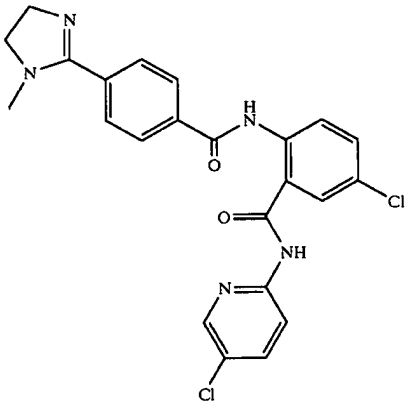
Example 80

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)-4,5-difluorophenylcarboxamide



This compound was prepared according to the procedure previously described. MS found for $C_{25}H_{18}BrF_2N_4O_4S$ $(M+H)^+$: 587.

Example 81



Step 1: To a solution of 2-amino-5-chloropyridine (328 mg, 2.55 mmol) in tetrahydrofuran (5 ml) was 0.5M potassium bis(trimethylsilyl)amide in toluene (10 ml, 5.05 mmol) dropwise at −78° C. After stirred for additional 0.5 hr at −78° C., the mixture was added 5-chloroisatoic anhydride (0.5 g, 2.55 mmol) at −78° C. The mixture was warmed up to r.t gradually and stirred overnight. After quenched by saturated ammonium chloride solution, the mixture was extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl)) carboxamide (0.71 g. 100%). MS found for Cl2H9Cl2N3O M^+=282, $(M+2)^+$=284.

Step 2: To a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71 g, 2.52 mmol) in dichloromethane (10 ml) was added 3-cyanobenzoly chloride (417 mg, 2.52 mmol) and pyridine (0.611 ml, 7.55 mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl (4-cyanophenyl)carboxamide

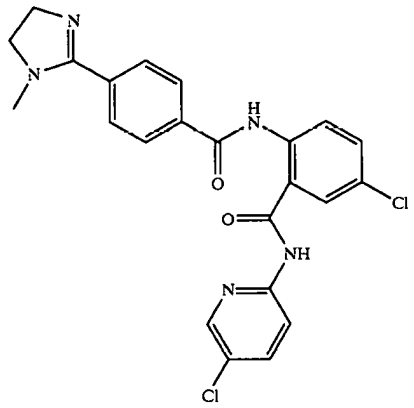
as a solid (683 mg, 66%). MS found for C20H12Cl2N4O2 M^+=411, $(M+2)^+$=413.

Step 3: To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (683 mg, 1.66 mmol) in anhydrous pyridine (10 ml) and triethyl amine (1 ml) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous acetone (5 ml) and iodomethane (1 ml, 16.6 mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the residue was dissolved in anhydrous methanol (5 ml) and added a solution of N-methylethylenediamine (0.732 ml, 8.3 mmol) and acetic acid (1.5 ml) in anhydrous methanol (5 ml). The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for C23H19Cl2N5O2 M^+=468 $(M+2)^+$=470.

Examples 82–106

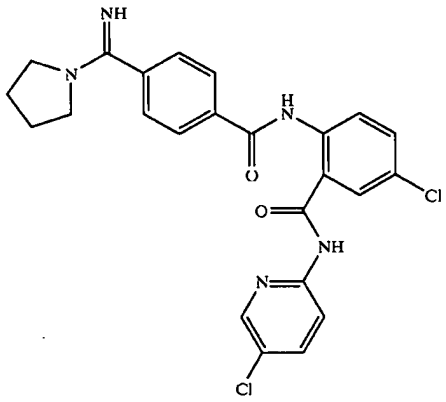
The following compounds were prepared according to the procedure previously described

Example 82



$C_{23}H_{19}Cl_2N_5O_2$
M+ = 468
(M+2)+ = 470

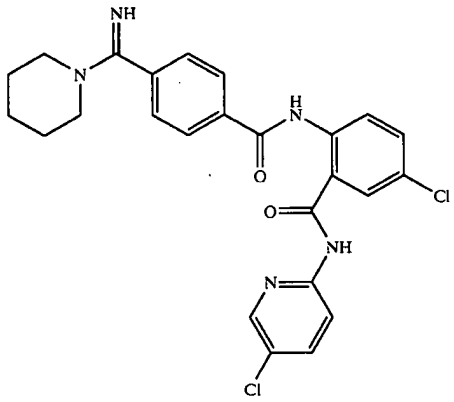
Example 83



$C_{24}H_{21}Cl_2N_5O_2$
M^+ = 482
(M+2)+ = 484

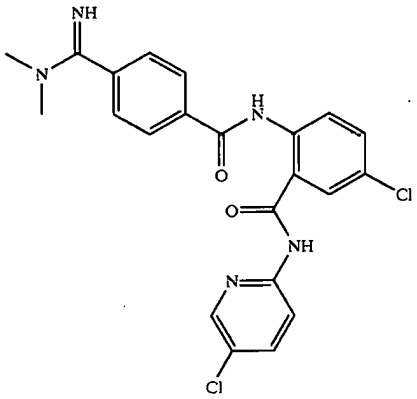
-continued

Example 84



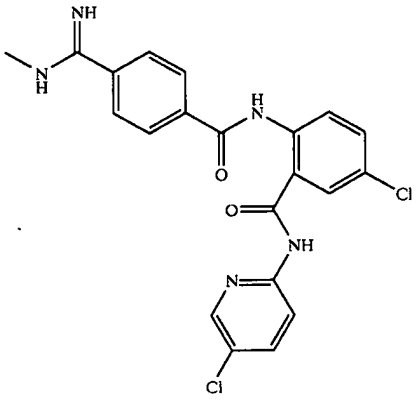
$C_{25}H_{23}Cl_2N_5O_2$
M^+ = 496
$(M+2)^+$ = 498

Example 85



$C_{22}H_{19}Cl_2N_5O_2$
M^+ = 456
$(M+2)^+$ = 458

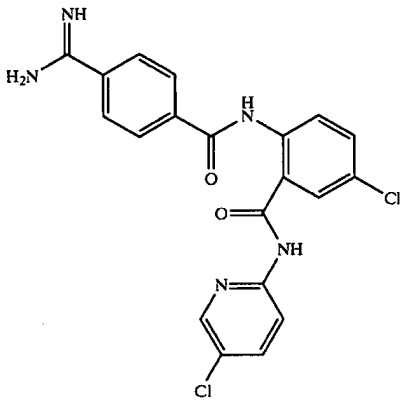
Example 86



$C_{21}H_{17}Cl_2N_5O_2$
M^+ = 442
$(M+2)^+$ = 444

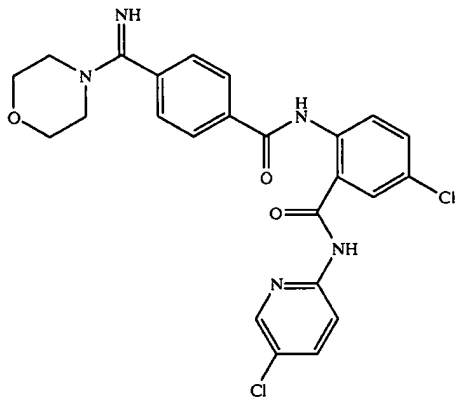
-continued

Example 87



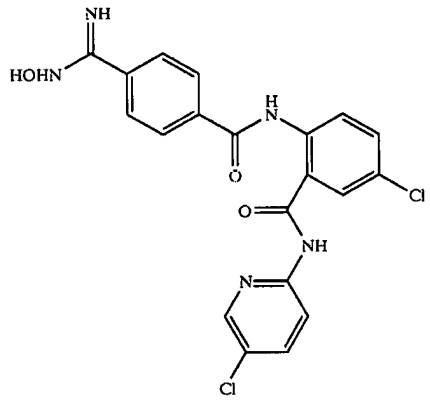
$C_{20}H_{15}Cl_2N_5O_2$
$M^+ = 428$
$(M+2)^+ = 430$

Example 88



$C_{24}H_{21}Cl_2N_5O_3$
$M^+ = 498$
$(M+2)^+ = 500$

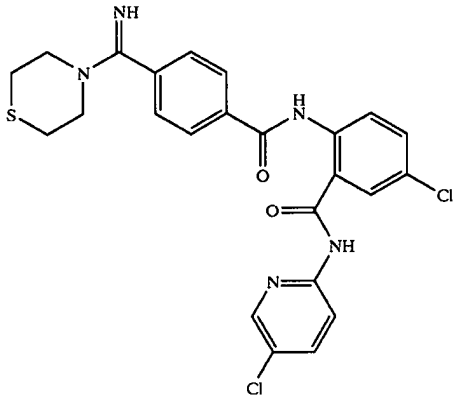
Example 89



$C_{20}H_{15}Cl_2N_5O_2$
$M^+ = 444$
$(M+2)^+ = 446$

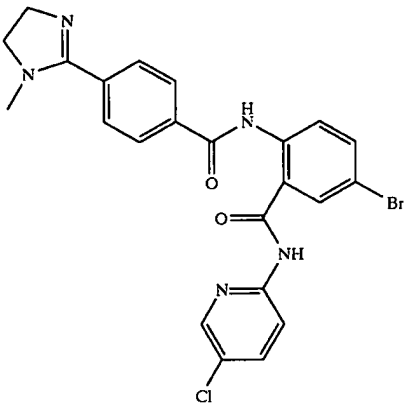
-continued

Example 90



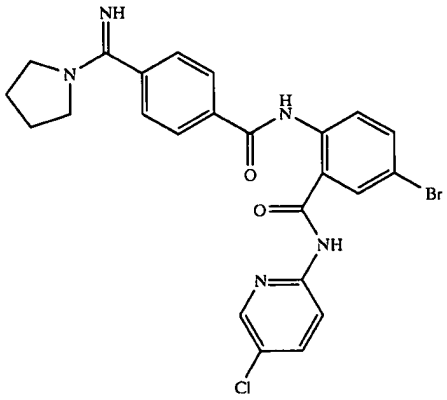
$C_{24}H_{21}Cl_2N_5O_2S$
$M^+ = 514$
$(M+2)^+ = 516$

Example 91



$C_{23}H_{19}BrClN_5O_2$
$M^+ = 512$
$(M+2)^+ = 514$

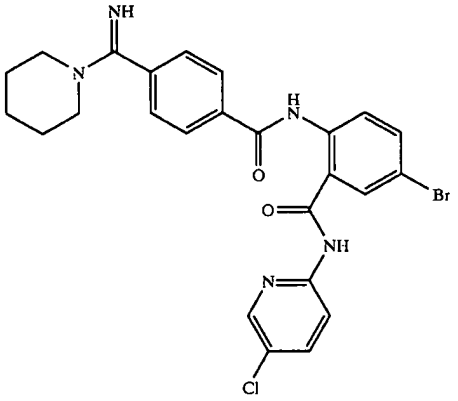
Example 92



$C_{24}H_{21}BrClN_5O_2$
$M^+ = 526$
$(M+2)^+ = 528$

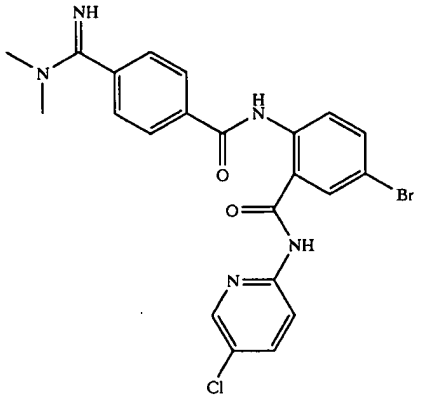
-continued

Example 93



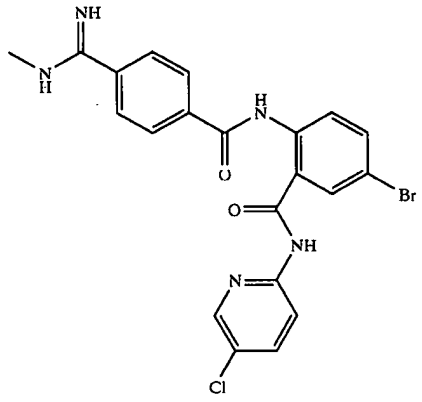
$C_{25}H_{23}BrClN_5O_2$
$M^+ = 540$
$(M+2)^+ = 542$

Example 94



$C_{22}H_{19}BrClN_5O_2$
$M^+ = 500$
$(M+2)^+ = 502$

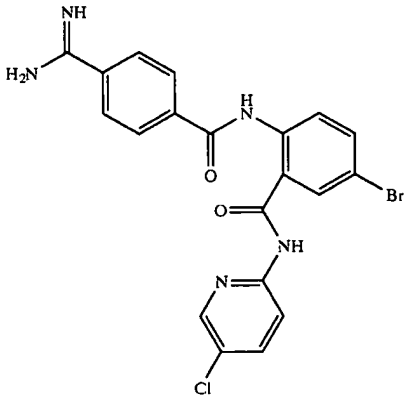
Example 95



$C_{21}H_{17}BrClN_5O_2$
$M^+ = 486$
$(M+2)^+ = 488$

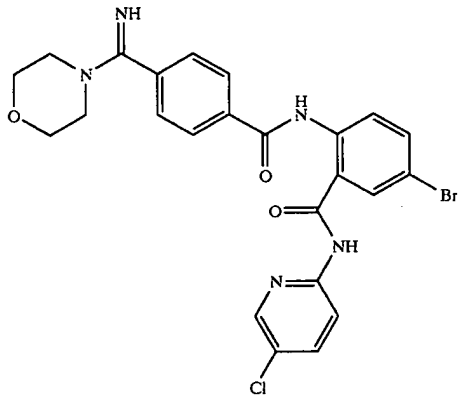
-continued

Example 96



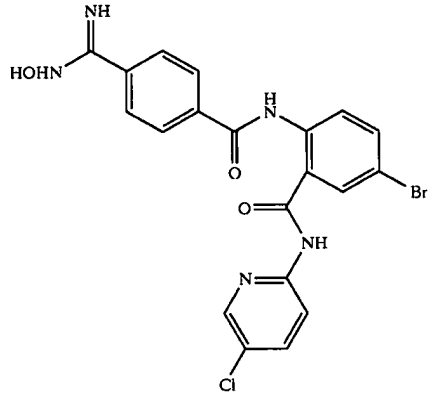
$C_{20}H_{15}BrClN_5O_2$
$M^+ = 472$
$(M+2)^+ = 474$

Example 97



$C_{24}H_{21}BrClN_5O_3$
$M^+ = 542$
$(M+2)^+ = 544$

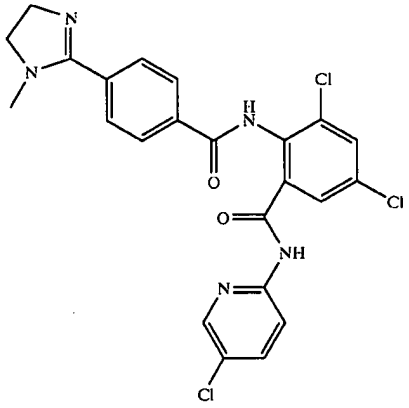
Example 98



$C_{20}H_{15}BrClN_5O_2$
$M^+ = 488$
$(M+2)^+ = 490$

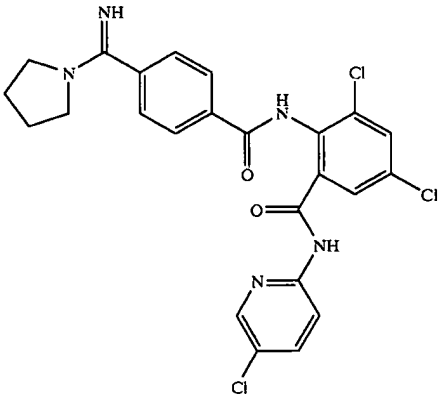
-continued

Example 99



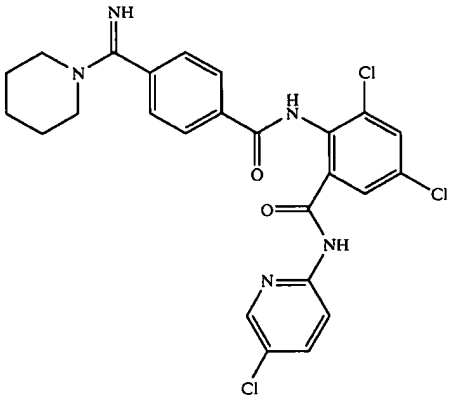
$C_{23}H_{18}Cl_3N_5O_2$
$M^+ = 502$
$(M+2)^+ = 504$

Example 100



$C_{24}H_{20}Cl_3N_5O_2$
$M^+ = 516$
$(M+2)^+ = 518$

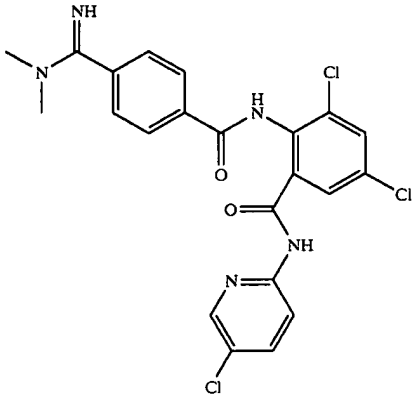
Example 101



$C_{25}H_{22}Cl_3N_5O_2$
$M^+ = 530$
$(M+2)^+ = 532$

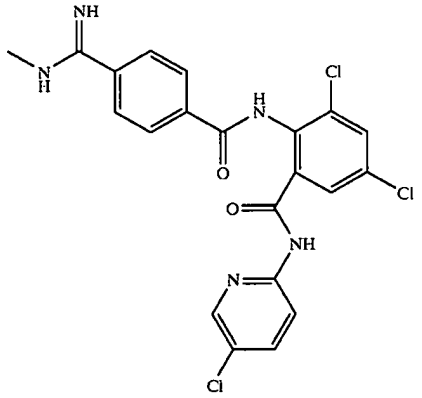
-continued

Example 102



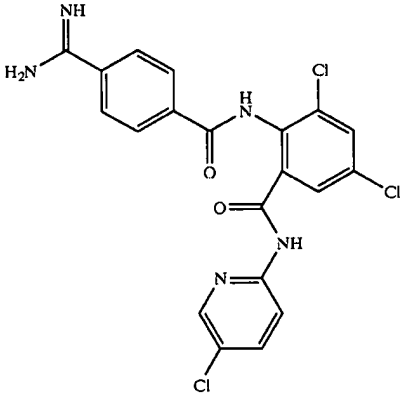
$C_{22}H_{18}Cl_3N_5O_2$
$M^+ = 490$
$(M+2)^+ = 492$

Example 103



$C_{21}H_{16}Cl_3N_5O_2$
$M^+ = 476$
$(M+2)^+ = 478$

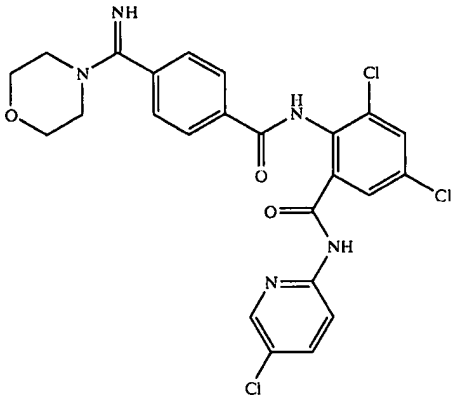
Example 104



$C_{20}H_{14}Cl_3N_5O_2$
$M^+ = 462$
$(M+2)^+ = 464$

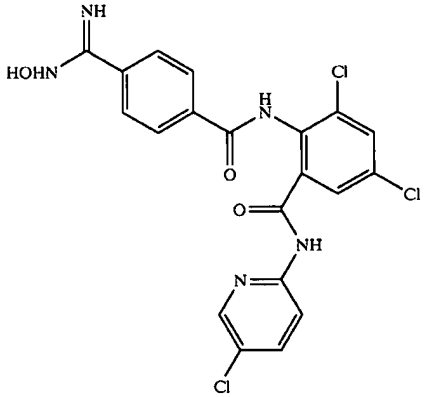
-continued

Example 105



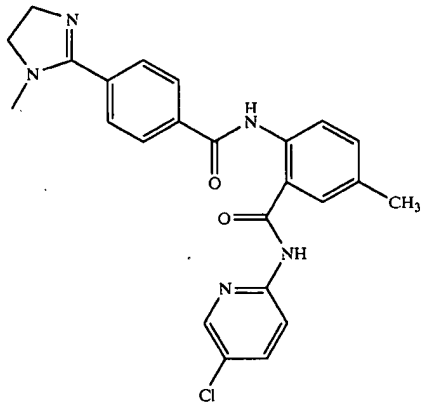
$C_{24}H_{20}Cl_3N_5O_2$
$M^+ = 432$
$(M+2)^+ = 534$

Example 106



$C_{20}H_{12}Cl_3N_5O_2$
$M^+ = 478$
$(M+2)^+ = 480$

Example 107



Step 1: To a solution of 5-methyl-2-nitrobenzoic acid (1 g, 5.52 mmol) in dichloromethane (5 ml) was added oxalyl chloride (0.964 ml, 11.04 mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5 ml). 2-amino-5-chloropyridine (852 mg, 6.62 mmol) and pyridine (1.34 ml, 16.56 mmol) were added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide as a solid (1.48 g, 92%). MS found for C13H10ClN3O3 M^+=291, $(M+2)^+$=293.

Step 2: To a solution of the compound of N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide (1.48 g, 5.1 mmol) in methanol (10 ml) was added 5% Pt/C (1.48 g, 0.19 mmol). The mixture was applied hydrogen balloon at r.t. for 2 hrs. After the filtration by Celite, the filtrate was concentrated to give (2-aminophenyl)-N-(2-pyridyl) carboxamide, C, chloride, N (1.36 g, 100%). MS found for C13H12ClN3O M^+=262, $(M+2)^+$=264.

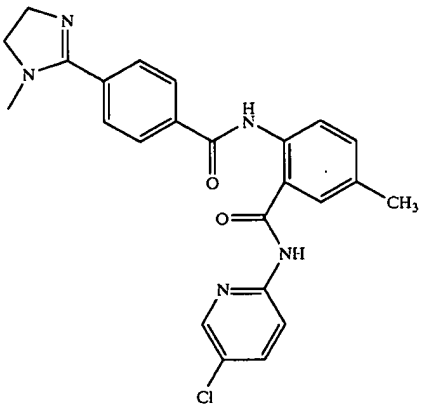
Step 3: To a solution of the compound of (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36 g, 5.2 mmol) in dichloromethane (10 ml) was added 3-cyanobenzoly chloride (860 mg, 5.2 mmol) and pyridine (1.26 ml, 15.6 mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide as a solid (830 mg, 41%). MS found for C21H15ClN4O2 M^+=390, $(M+2)^+$=392.

Step 4: To a lotion of the compound of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}(4-cyanophenyl)carboxamide (830 mg, 2.1 mmol) in anhydrous methanol (5 ml) and ethyl acetate (10 ml) was saturated with hydrogen chloride gas at 0° C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous methanol (5 ml) and N-methylethylenediamine (0.926 ml, 10.5 mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for C24H22ClN5O2 M^+=448, $(M+2)^+$=450.

Examples 108–113

The following compounds were prepared according to the procedure previously described

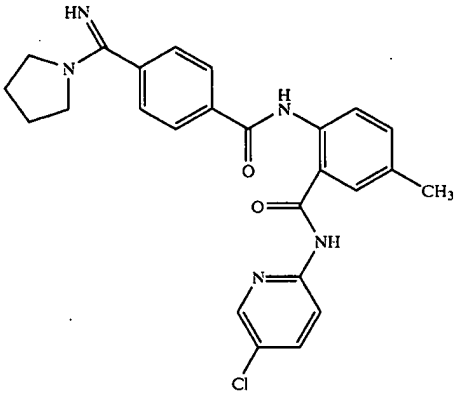
Example 108



$C_{24}H_{22}ClN_5O_2$
$M^+ = 448$
$(M+2)^+ = 450$

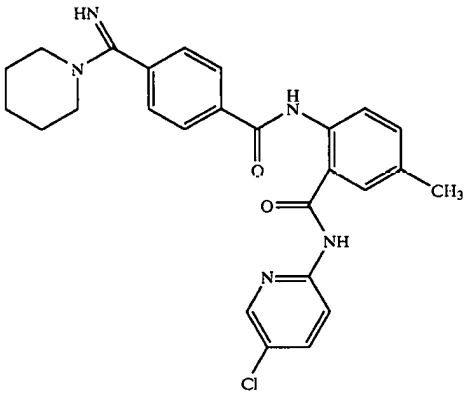
-continued

Example 109



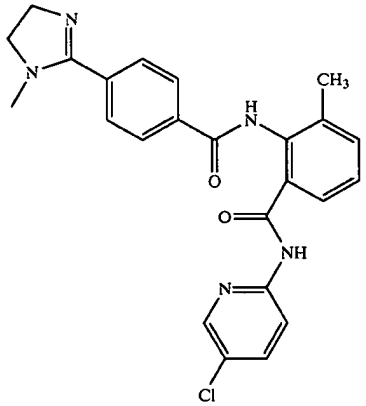
$C_{25}H_{24}ClN_5O_2$
$M^+ = 462$
$(M+2)^+ = 464$

Example 110



$C_{26}H_{26}ClN_5O_2$
$M^+ = 476$
$(M+2)^+ = 478$

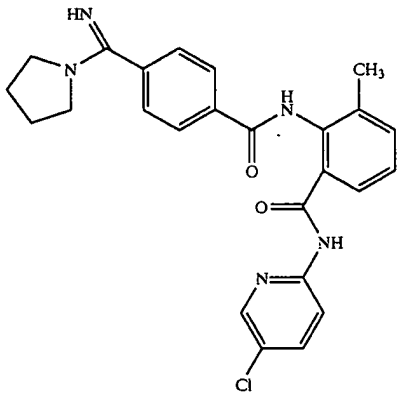
Example 111



$C_{24}H_{22}ClN_5O_2$
$M^+ = 448$
$(M+2)^+ = 450$

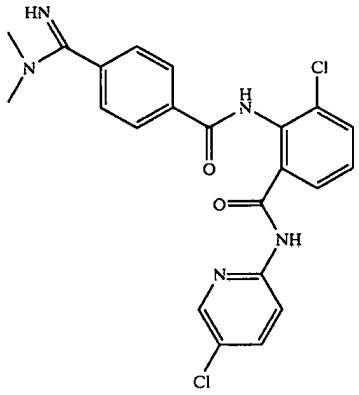
-continued

Example 112



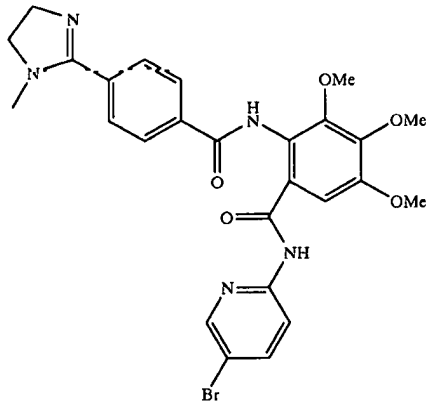
$C_{25}H_{24}ClN_5O_2$
$M^+ = 462$
$(M+2)^+ = 464$

Example 113



$C_{23}H_{22}ClN_5O_2$
$M^+ = 436$
$(M+2)^+ = 438$

Example 114



Step 1: To a solution of 3,4,5-trimethoxy-2-nitrobenzoic acid (0.5 g, 1.95 mmol) in dichloromethane (5 ml) was added oxalyl chloride (0.34 ml, 3.9 mmol) and a few drops of dimethylformamide. The mixture was stirred at

r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5 ml). 2-amino-5-bromopyridine (0.81 g, 4.7 mmol) and pyridine (0.94 ml, 11.7 mmol)were added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide as a solid (790 mg, 98%). MS found for C15H14BrN3O6 M^+=412, $(M+2)^+$=414.

Step 2: To a solution of the compound of N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide (790 mg, 1.92 mmol) in ethyl acetate (5 ml) was added tin chloride (II) hydrate (1.73 g, 7.67 mmol). The mixture was stirred under reflux condition for 2 hrs. After filtered by Celite, the filtrate was added 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570 mg, 77%). MS found for C15H16BrN3O4 M^+=382, $(M+2)^+$=384.

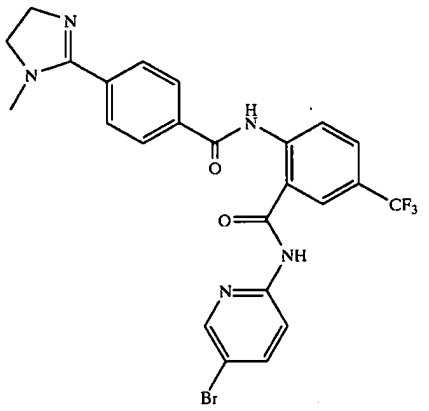
Step 3: To a solution of the compound of (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570 mg; 1.49 mmol) in dichloromethane (5 ml) was added 3-cyanobenzoly chloride (247 mg, 1.49 mmol) and pyridine (0.362 ml, 4.48 mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-{6-[N-(5-bromo(2-pyridyl)) carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl) carboxamide as a solid (680 mg, 69%). MS found for C23H19BrN4O5 M^+=511, $(M+2)^+$=513.

Step 4: To a lotion of the compound of N-{6-[N-(5-bromo (2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}(4-cyanophenyl)carboxamide (680 mg, 1.33 mmol) in anhydrous methanol (5 ml) and ethyl acetate (10 ml) was saturated with hydrogen chloride gas at 0° C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous methanol (5 ml) and N-methylethylenediamine (0.586 ml, 6.65 mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl}[4-(1-methyl(2-imidazolin-2-yl)) phenyl]carboxamide as a white powder (240 mg, 32%). MS found for C26H26BrN5O5 M^+=568, $(M+2)^+$=570.

Examples 115–118

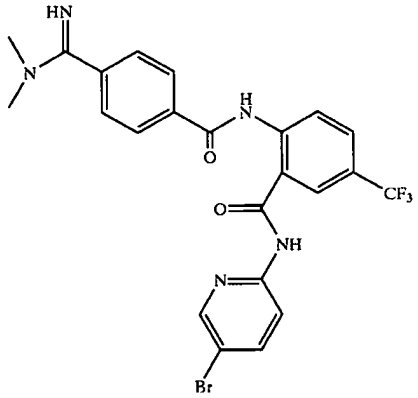
The following compounds were prepared according to the procedure previously described

Example 115



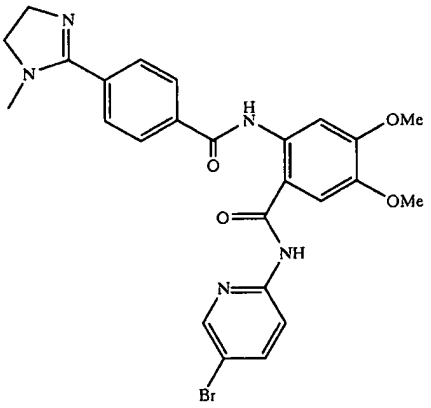
$C_{24}H_{19}BrF_3N_5O_2$
$M^+ = 546$
$(M+2)^+ = 548$

Example 116



$C_{23}H_{19}BrF_3N_5O_2$
$M^+ = 534$
$(M+2)^+ = 536$

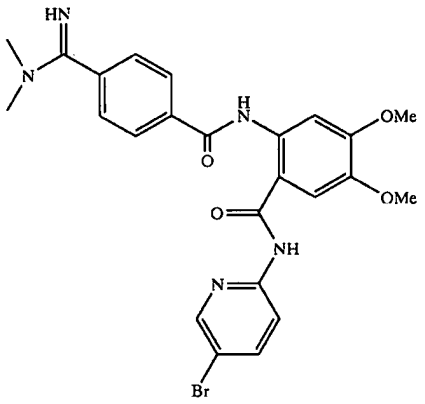
Example 117



$C_{25}H_{24}BrN_5O_4$
$M^+ = 494$
$(M+2)^+ = 496$

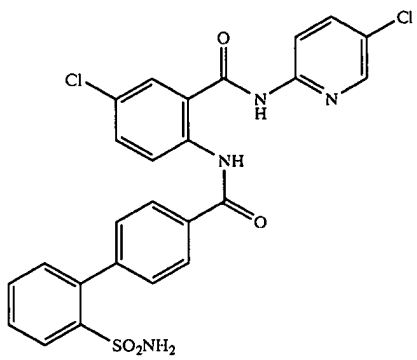
-continued

Example 118



$C_{24}H_{24}BrN_5O_2$
$M^+ = 482$
$(M+2)^+ = 484$

Example 119

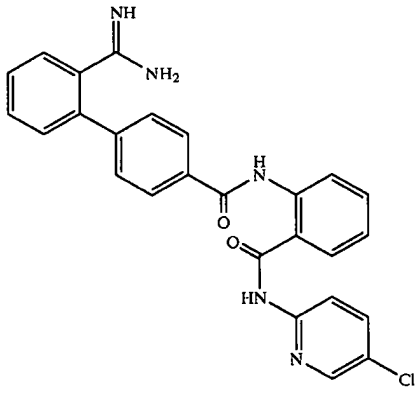


Step 1: To a solution of 4-{2-{[(tert-butyl) amino}sulfonyl}phenyl}benzoic acid (167 mg, 0.5 mmol) in dichloromethane (5 ml) was added oxalyl chloride (0.09 ml, 1 mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5 ml). The compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.17 g, 0.6 mmol) and pyridine (0.122 ml, 1.5 mmol) were added to the solution. The mixture was stirred at r.t. overnight. The solvent was evaporated to give (2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]-carbonylamino}-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide. MS found for C29H26Cl2N4O4S M^+=597, $(M+2)^+$=599.

Step 2: The mixture of the compound of (2-{[4-(2-{[(tert-butyl)amino]sulfonyl}phenyl)phenyl]carbonylamino}-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide example 12 (0.5 mmol) in trifluoroacetic acid (5 ml) was stirred at r.t. for 5 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-(5-chloro(2-pyridyl))(5-chloro-2-{[4-(2-sulfamoylphenyl)-phenyl]carbonylamino}phenyl)-carboxamide as a white powder (68 mg, 25%). MS found for C25H18Cl2N4O4S M^+=541, $(M+2)^+$=543.

Example 120

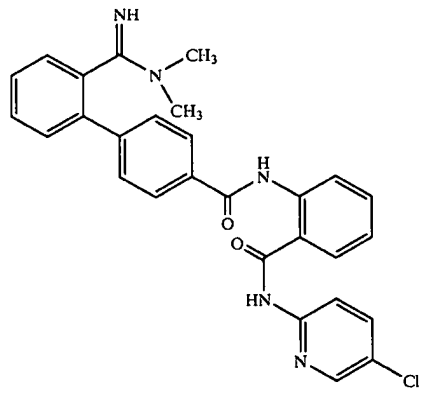
2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl] phenyl}carbamoyl)phenyl]-benzenecarboxamidine



A stream of H_2S (g) was bubbled through a 0° C. solution of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl]carboxamide (100 mg, 0.22 mmol, 1.0 (equiv.) in 9 mL pyridine and 1 mL NEt_3 until saturation. The mixture was stirred at rt for 1 day and evaporated. The resulting residue was treated with MeI (94 mg, 0.663 mmol, 3.0 equiv.) in 10 mL acetone at reflux temperature for 1 hr and concentrated to dryness. The resulting residue was treated with a mixture of NH_4OAc (340 mg, 4.42 mmol, 20 equiv.) in 0.5 mL acetic acid and 2 mL methanol at 50° C. for 2 days. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}-carbamoyl)phenyl]benzenecarboxamidine (15 mg, 15%). MS found for $C_{26}H_{20}ClN_5O_2$ $(M+H)^+$: 470.

Example 121

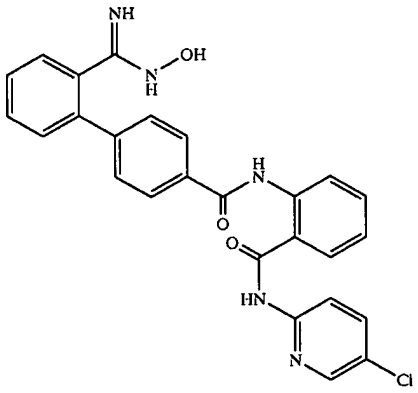
(4-{2-1(dimethylamino)iminomethyl] phenyl}phenyl)-N-{2-[N-(5-chloro(2-pyridyl)) carbamoyl]phenyl}carboxamide



This compound was prepared according to the procedure previously described. MS found for $C_{28}H_{24}ClN_5O_2$ $(M+H)^+$: 498.

Example 122

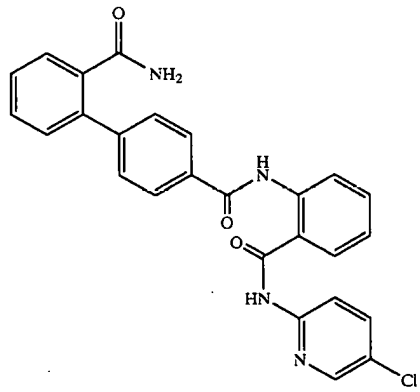
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl)-phenyl]phenyl}carboxamide



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl]carboxamide (14 mg, 0.03 mmol, 1.0 equiv.), hydroxyamine hydrochloride (6.25 mg, 0.09 mmol, 3.0 equiv.) and triethyl amine (0.03 mL, 0.3 mmol, 10.0 equiv.) in ethanol (3 mL) was stirred at rt for 6 days, concentrated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl)phenyl]phenyl}carboxamide (4 mg, 27.5%). MS found for $C_{26}H_{20}ClN_5O_3$ $(M+H)^+$: 486.

Example 123

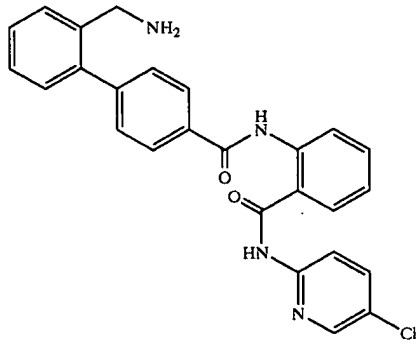
2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzamide



This compound was obtained as one of the side product in Example 122. MS found for $C_{26}H_{19}ClN_4O_3$ $(M+H)^+$: 471

Example 124

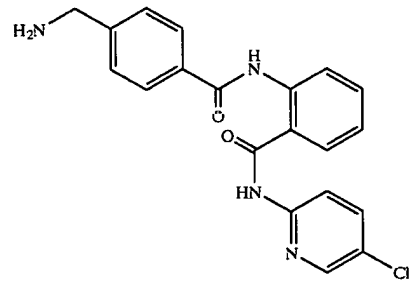
{4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-phenyl}carboxamide



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl]carboxamide (200 mg, 0.442 mmol, 1.0 equiv.), cobalt chloride (86 mg, 0.664 mmol, 1.5 equiv.) and sodium borohydride (50 mg, 1.33 mmol, 3.0 equiv.) in DMF (15 mL) was stirred at 0° C. to rt for 3 days. The reaction was quenched with ice cubes, diluted with DCM (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave {4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (87 mg, 43%). MS found for $C_{26}H_{21}ClN_4O_2$ $(M+H)^+$: 457

Example 125

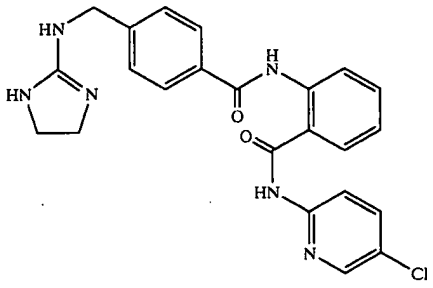
[4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (1 g, 2.6 mmol, 1.0 equiv.), cobalt chloride (0.5 g,. 3.85 mmol, 1.5 equiv.) and sodium borohydride (0.295 g, 7.8 mmol, 3.0 equiv.) in DMF (20 mL) was stirred at 0° C. to rt for 2.5 hr. The reaction was quenched with ice cubes, diluted with ethyl acetate (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (320 mg, 30%). MS found for $C_{20}H_{17}ClN_4O_2$ $(M+H)^+$: 381.

Example 126

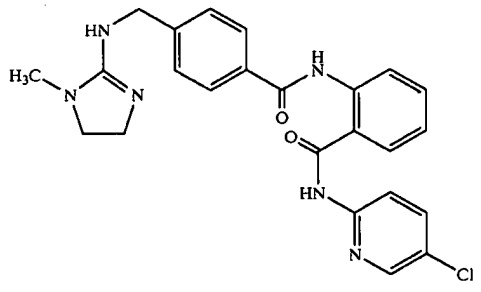
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]-phenyl}carboxamide



A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro (2-pyridyl))carbamoyl]phenyl}carboxamide (80 mg, 0.21 mmol), 2-methylthio-2-imidazoline hydriodide (77 mg, 0.315 mmol, 1.5 equiv.) and triethyl amine (0.5 mL) in 1 mL DMF was stirred at room temperature overnight, concentrated to dryness and HPLC (C18 reversed phase) eluting with 0.1% TFA in H_2O/CH_3CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino) methyl]phenyl}carboxamide (13.5 mg, 15%). MS found for $C_{23}H_{21}ClN_6O_2$ $(M+H)^+$: 449

Example 127

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino] methyl}phenyl)carboxamide

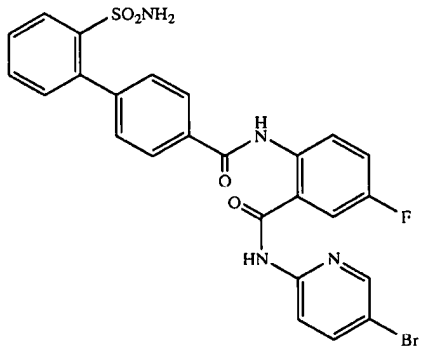


Step 1: To the boiling solution of 2-methylthio-2-imidazoline hydriodide (1 g, 8.4 mmol) in methanol (10 mL) was added MeI (0.78 mL, 12.6 mmol, 1.5 equiv.) dropwise. The reaction mixture was stirred at reflux temperature for 1 hr, concentrated and crystallized with ether to give 1-methyl-2-methylthio-2-imidazoline (1.1 g, 100%). MS found for $C_5H_{10}N_2S$ $(M+H)^+$: 131.

Step 2: A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (74 mg, 0.195 mmol), 1-methyl-2-methylthio-2-imidazoline (25 mg, 0.195 mmol), NEt3 (2 mL) and pyridine (5 mL) was stirred at 80° C. overnight, concentrated and HPLC (C18 reversed phase)eluting with 0.1% TFA in H2O/CH3CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl] phenyl}(4-{[(1-methyl(2-imidazolin-2-yl))amino] methyl}phenyl)carboxamide (52 mg, 65%). MS found for $C_{24}H_{23}ClN_6O_2$ $(M+H)^+$: 463.

Example 128

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)-5-. fluorophenylcarboxamide.

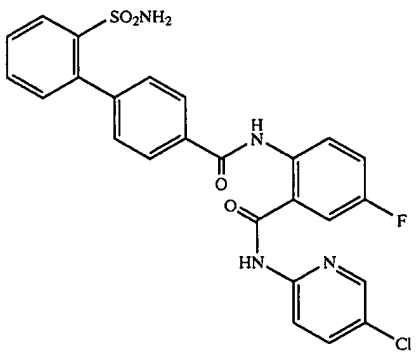


Step 1: A solution of 5-fluoro-2-nitrobenzoic acid (10.0 g, 54 mmol, 1.0 equiv), 2-amino-5-bromopyridine (12.2 g, 1.3 equiv), in 80 mL of pyridine was treated with phosphorous oxychloride (25.3 g, 3.0 equiv) for 30 min. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The volatile was evaporated, and the product was triturated with diethyl ether to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (12.5 g, 68%). MS found for $C_{12}H_7BrFN_3O_3$ $(M+H)^+$: 340, 342.

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-flurophenylcarboxamide (2.0 g, 5.88 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with $SnCl_22H_2O$ (5.90 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (1.79 g, 98%). MS found for $C_{12}H_9BrFN_3O$ $(M+H)^+$: 310, 312.

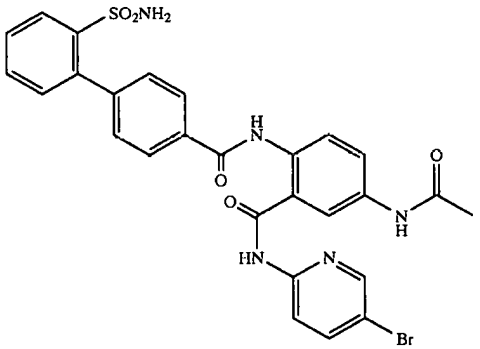
Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.310 g, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (0.430 g, 1.3 equiv), pyridine (2 mL) in 10 mL of dichloromethane was stirred at rt overnight The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was triturated with diethyl ether, and then with chloroform to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)-5-fluorophenylcarboxamide (120 mg, 21%). MS found for $C_{25}H_{18}BrFN_4O_4S$ $(M+H)^+$: 569, 571.

Example 129



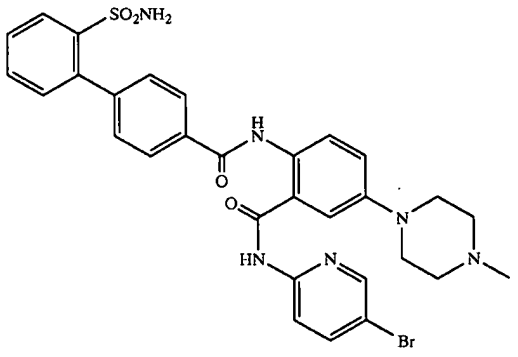
This compound was prepared according to the procedure described in example 2 with the exception of using zinc in acetic acid to reduce nitro-intermediate in step 2. The final product was purified by HPLC (C18 reversed phase)eluting with 0.5% TFA in H_2O/CH_3CN. MS found for $C_{25}H_{18}ClFN_4O_4S$ $(M+H)^+$: 525, 527.

Example 130



This compound was prepared according to the procedure described in example 2 with the exception of using 5-acetamido-2-nitrobenzoic acid as the starting material in step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{27}H_{22}BrN_5O_5S$ $(M+H)^+$: 608, 610.

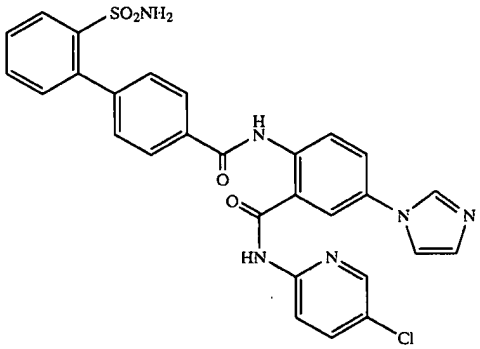
Example 131



This compound is prepared according to the procedure described in example 2 with the exception of the following step 1b performed on the nitro-intermediate from step 1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{30}H_{29}BrN_6O_4S$ $(M+H)^+$: 649, 651.

Step 1b: A mixture of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (0.68 g, 2 mmol, 1.0 equiv), N-methylpiperazine (0.60 g, 3 equiv), and Cs_2CO_3 (1.30 g, 2 equiv) in 5 mL of dimethylformamide was stirred at 90° C. overnight. Ethyl acetate was added and washed with H_2O. The organic layer was dried over Na_2SO_4, filtered, evaporated, purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-(4-N-methylpiperazine)phenylcarboxamide (0.54 g, 65%). MS found for $C_{17}H18BrN_5O_3$ $(M+H)^+$: 419, 421.

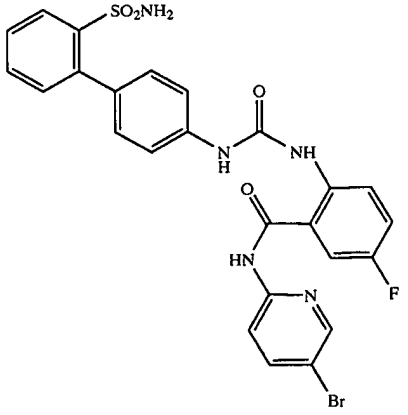
Example 132



This compound was prepared according to the procedure described in example 5. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN MS found for $C_{28}H_{21}ClN_6O_4S$ $(M+H)^+$: 573, 575.

Example 133

N-(5-bromo-2-pyridinyl)-(2-1-[(2-aminosulfonyl) phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide.

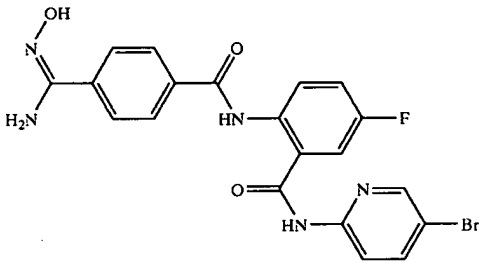


Step 3: A mixture of 4-[(2-t-butylaminosulfonyl)phenyl] phenylamine (0.180 g, 1.2 equiv), N,N'-disuccinimidyl carbonate (0.154 g, 1.2 equiv), 4-methylmorpholine (0.5 mL) in 10 mL of acetonitrile was stirred at rt for 30 min. N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.155 g, 0.5 mmol, 1.0 equiv) was added and the solution was stirred at rt for 3 hrs. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide (0.053 g, 18%). MS found for $C_{25}H_{19}BrFN_5O_4S$ $(M+H)^+$: 584, 586.

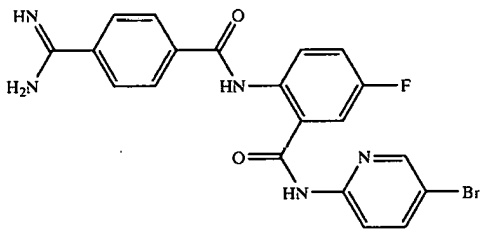
Examples 134–135

N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide.

Example 134



Example 135



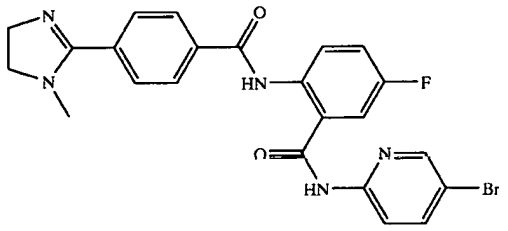
Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)5-fluorophenylcarboxamide (1.24 g, 4 mmol, 1.0 equiv), 4-cyano benzoyl chloride (0.792 g, equiv), and pyridine (3 mL) in 15 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.14 g, 65%). MS found for $C_{20}H_{12}BrFN_4O_2$ $(M+H)^+$: 439, 441.

Step 2: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.12 g, 2.56 mmol, 1.0 equiv), hydroxylamine-HCl (0.213 g, 1.2 equiv), and triethylamine (1 mL) in 15 mL of ethyl alcohol was stirred at 50° C. overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (compound Example 194) (0.84 g, 70%). One third of this material was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to yield 0.20 grams (71%). MS found for $C_{20}H_{15}BrFN_5O_3$ $(M+H)^+$: 472, 474.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (0.56 g, 1.19 mmol, 1.0 equiv) and zinc dust (0.39 g, 5.0 equiv), in 10 mL of acetic acid was stirred at rt for 45 min. The volatile was filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN give N-(5-bromo-2-pyridinyl)-(2-(4-arnidinophenylcarbonyl)amino)5-fluorophenyl-carboxamide (compound Example 195) (0.24 g, 44%). MS found for $C_{20}H_{15}BrFN_5O_2$ $(M+H)^+$: 456, 458.

Example 136

N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide.

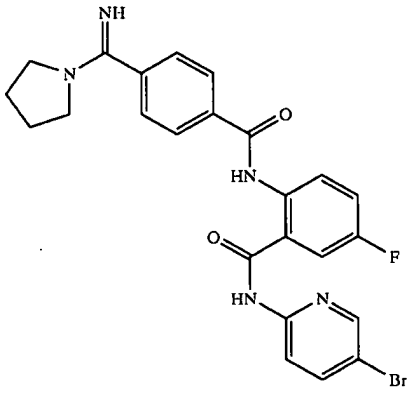


Step 1: A stream of HCl(g) was bubbled through a 0° C. solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.0 g, 2.3 mmol) in 30 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. One-fifth of the resulting residue was treated with (2-aminoethyl) methylamine (0.10 g) in 10 ml methanol at rt overnight. The solvent was removed at reduced pressure and the crude product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide (0.082 g, 37%). MS found for $C_{23}H_{19}BrFN_5O_2$ $(M+H)^+$: 496, 498.

Examples 137–198

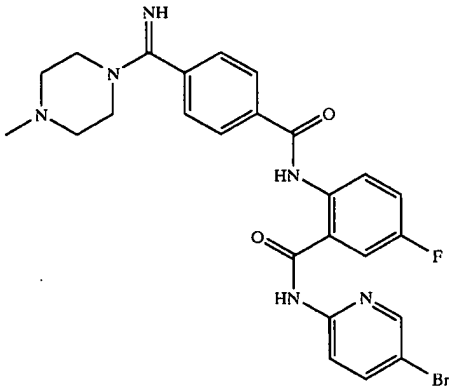
The following compounds were prepared generally according to the procedure described in Example 196.

Example 137



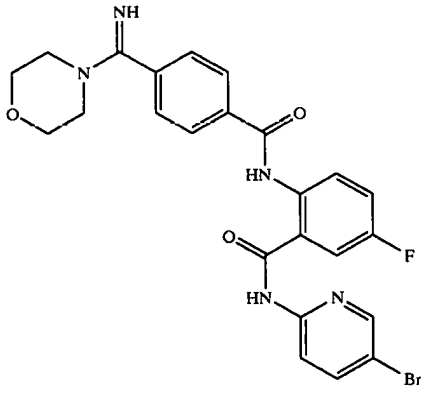
MS (M+H):510, 512

Example 138



MS (M+H):539, 541

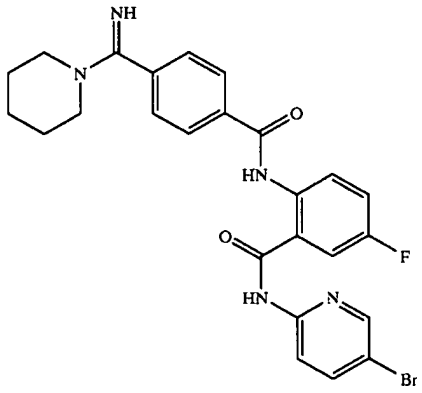
Example 139



MS (M+H):526, 528

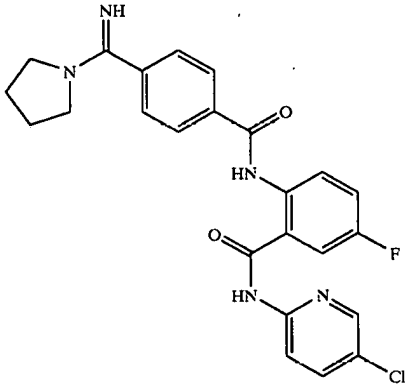
-continued

Example 140



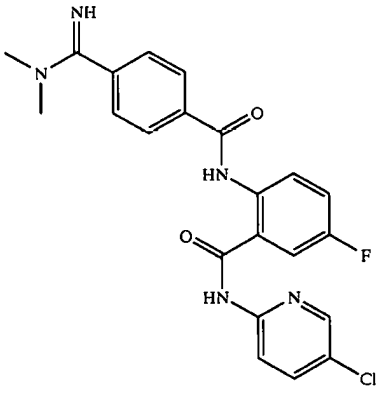
MS (M+H):524, 526

Example 141



MS (M+H):466, 468

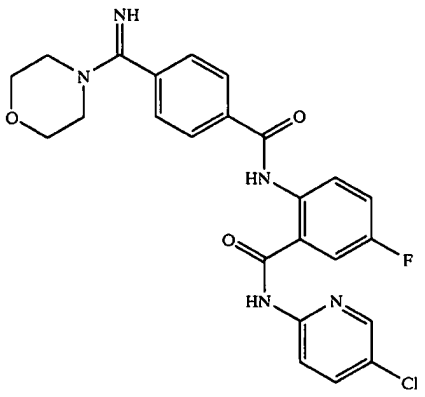
Example 142



MS (M+H):440, 442

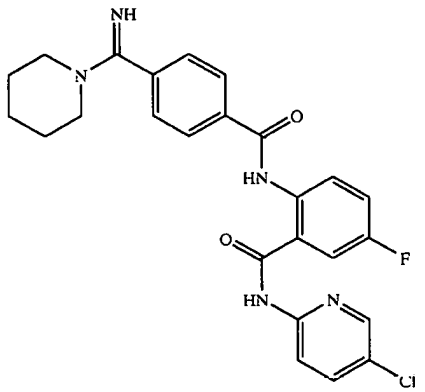
-continued

Example 143



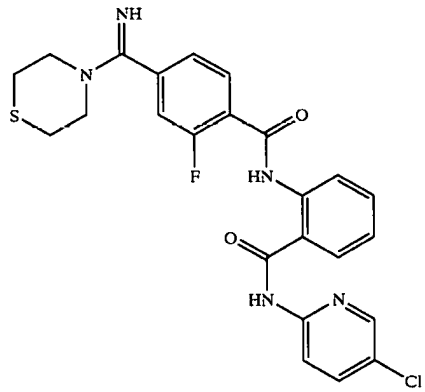
MS (M+H):482, 484

Example 144



MS (M+H):480, 482

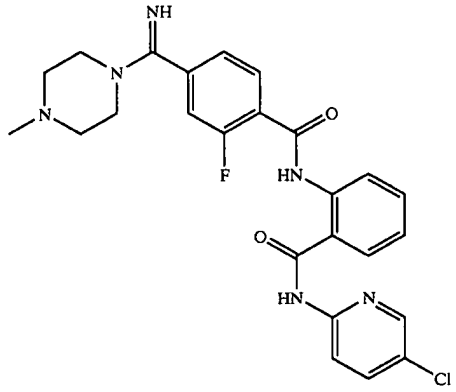
Example 145



MS (M+H):498, 500

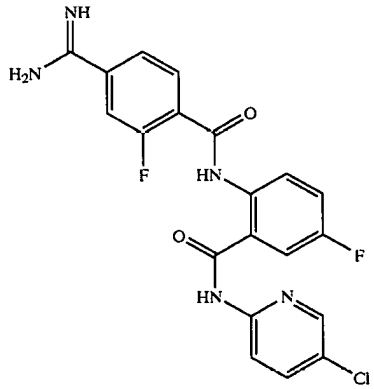
-continued

Example 146



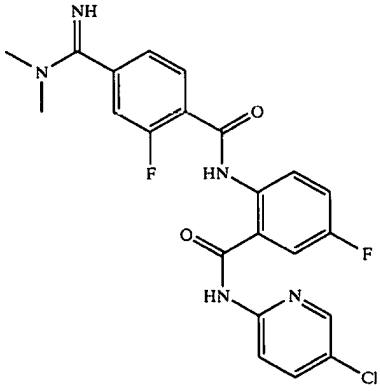
MS (M+H):495, 497

Example 147



MS (M+H):430, 432

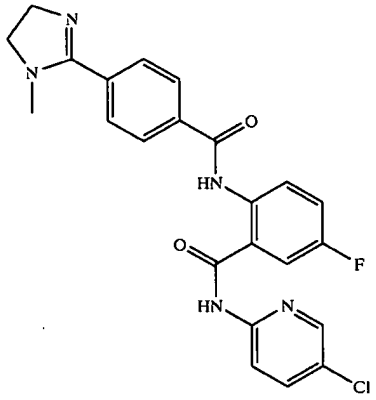
Example 148



MS (M+H):458, 460

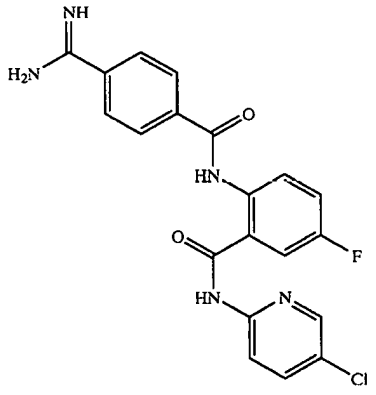
-continued

Example 149



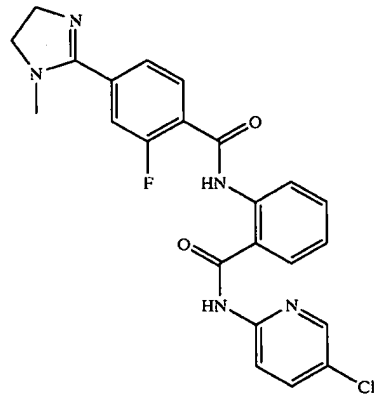
MS (M+H):452, 454

Example 150



MS (M+H):412, 414

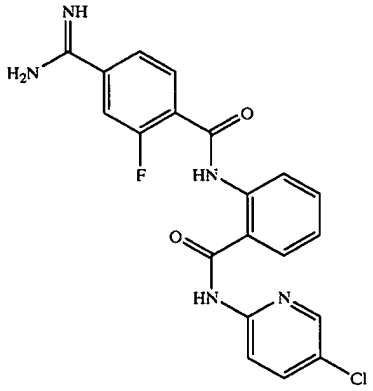
Example 151



MS (M+H):452, 454

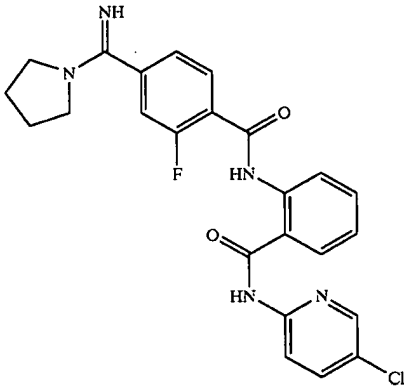
-continued

Example 152



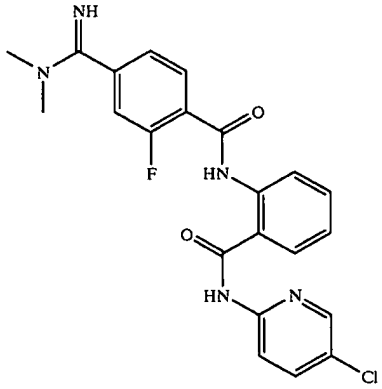
MS (M+H):412, 414

Example 153



MS (M+H):466, 468

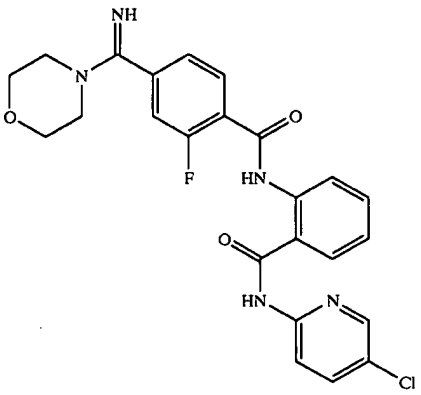
Example 154



MS (M+H):440, 442

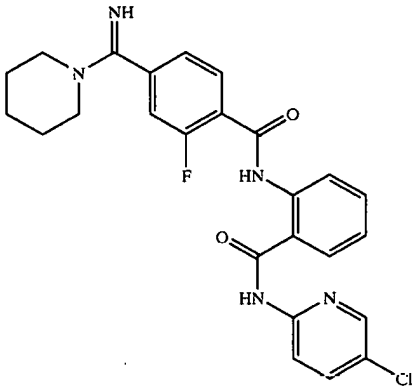
-continued

Example 155



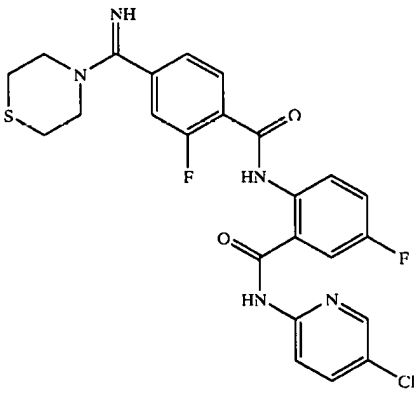
MS (M+H):482, 484

Example 156



MS (M+H):480, 482

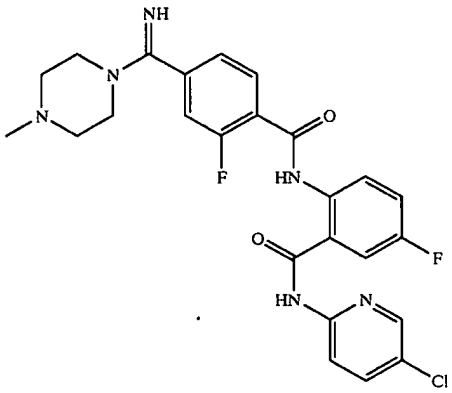
Example 157



MS (M+H):516, 518

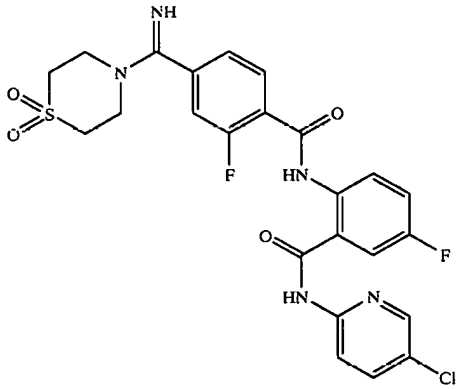
-continued

Example 158



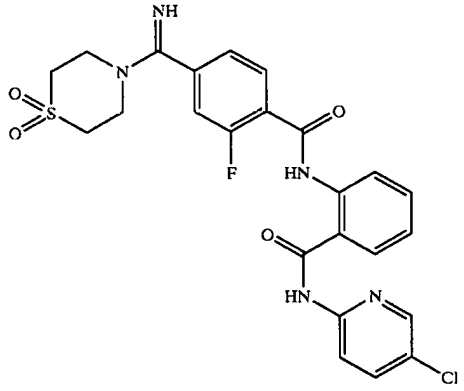
MS (M+H):513, 515

Example 159



MS (M+H):548, 550

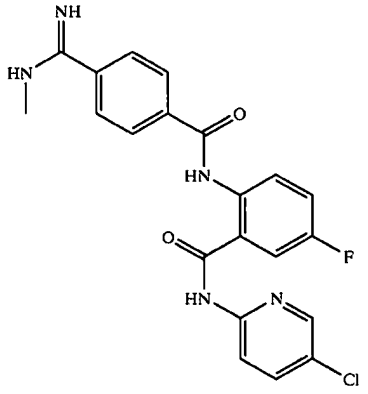
Example 160



MS (M+H):530, 532

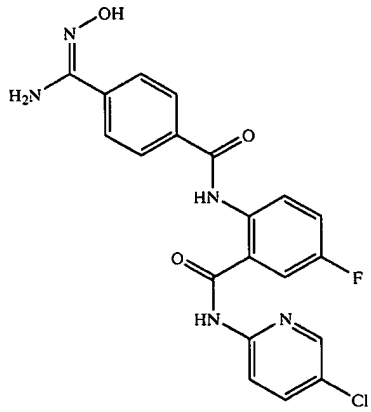
-continued

Example 161



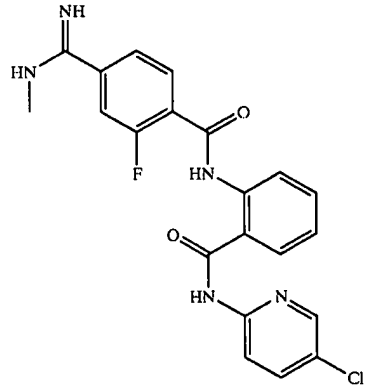
MS (M+H):426, 428

Example 162



MS (M+H):428, 430

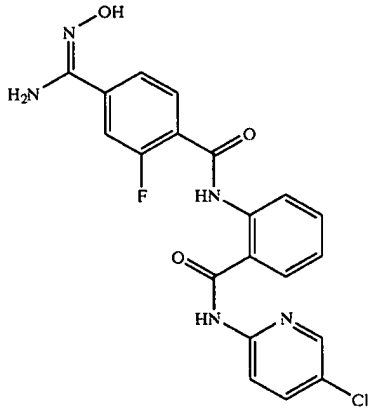
Example 163



MS (M+H):426, 428

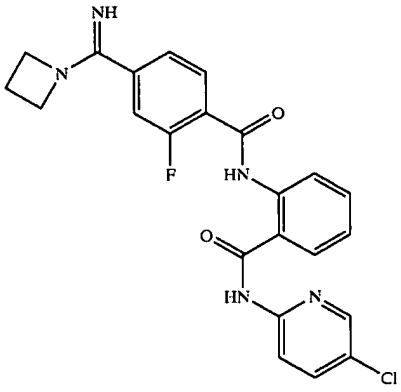
-continued

Example 164



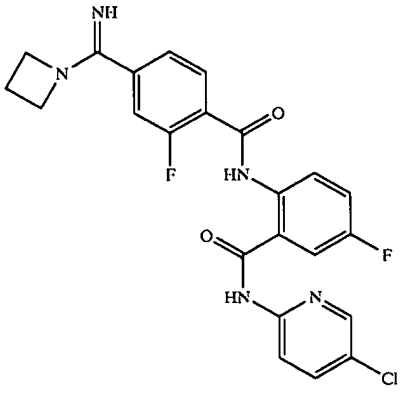
MS (M+H):428, 430

Example 165



MS (M+H):452, 454

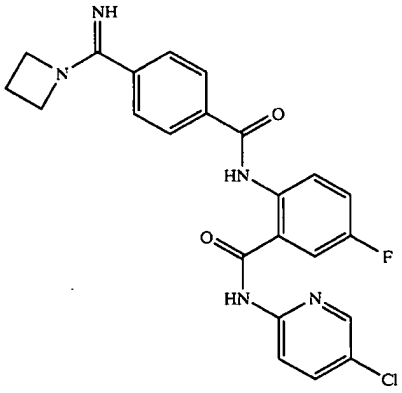
Example 166



MS (M+H):470, 472

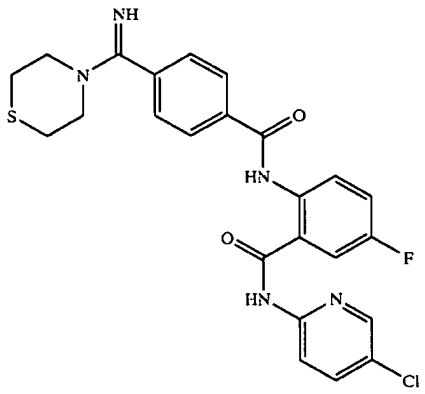
-continued

Example 167



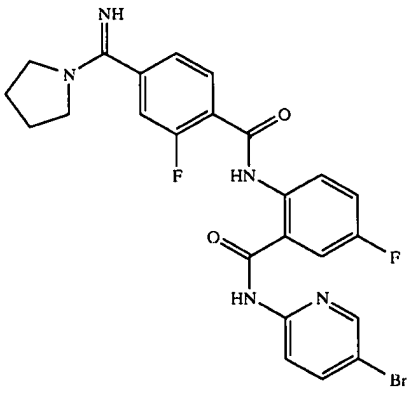
MS (M+H):452, 454

Example 168



MS (M+H):498, 500

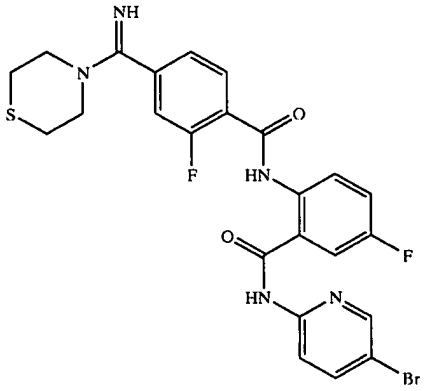
Example 169



MS (M+H):528, 530

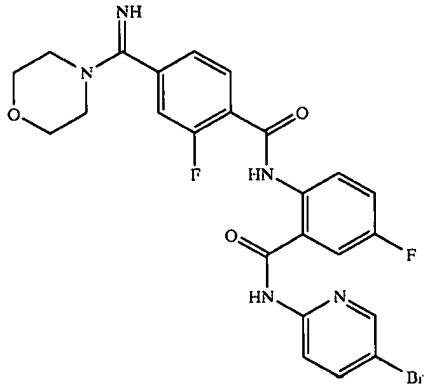
-continued

Example 170



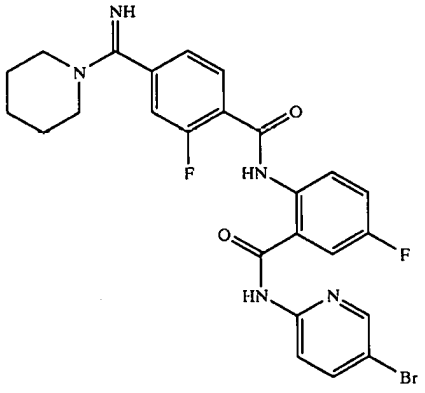
MS (M+H):560, 562

Example 171



MS (M+H):544, 546

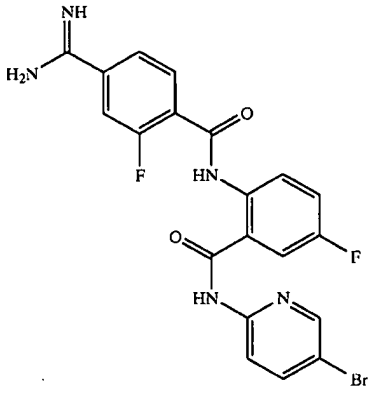
Example 172



MS (M+H):542, 544

-continued

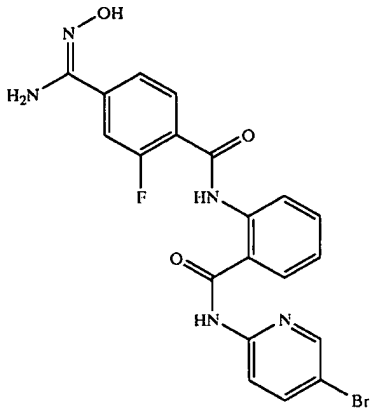
Example 173



MS (M+H):474, 476

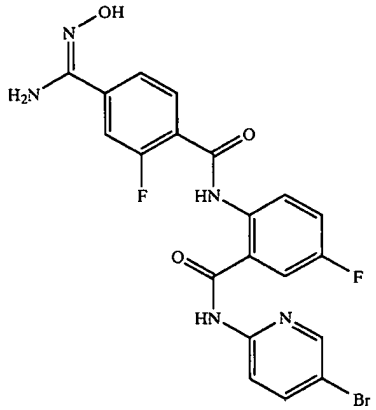
-continued

Example 176



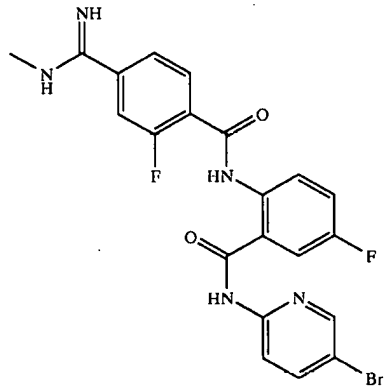
MS (M+H):472, 474

Example 174



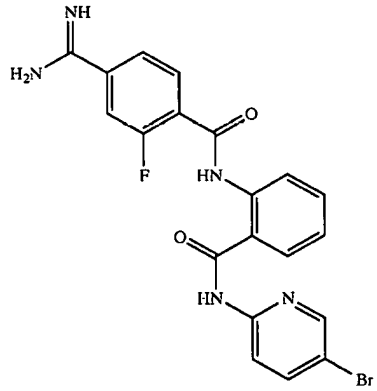
MS (M+H):490, 492

Example 177



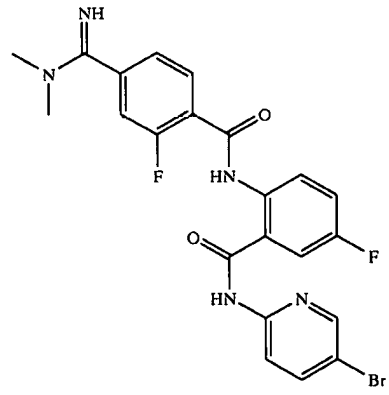
MS (M+H):488, 490

Example 175



MS (M+H):456, 458

Example 178



MS (M+H):502, 504

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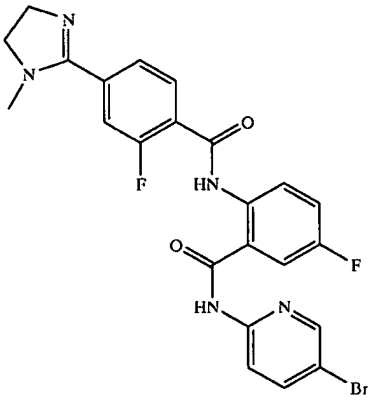
Example 179



MS (M+H):514, 516

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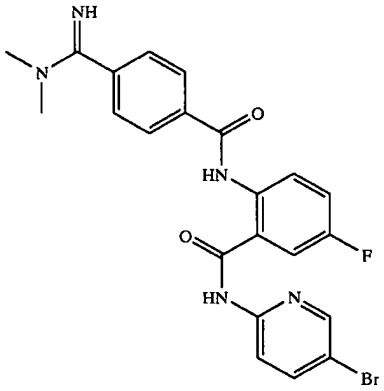
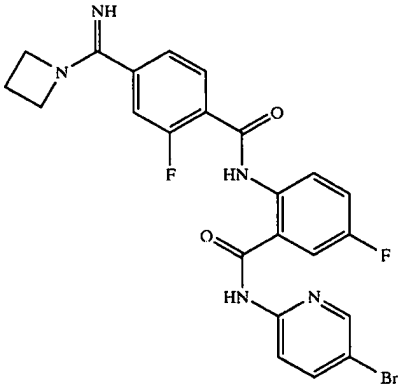
Example 182



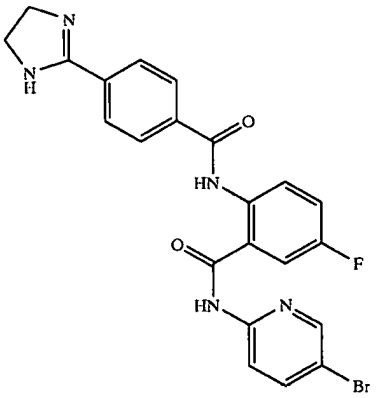
MS (M+H):484, 486

Example 180



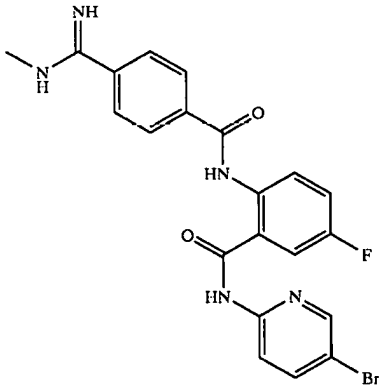
MS (M+H):514, 516

Example 183



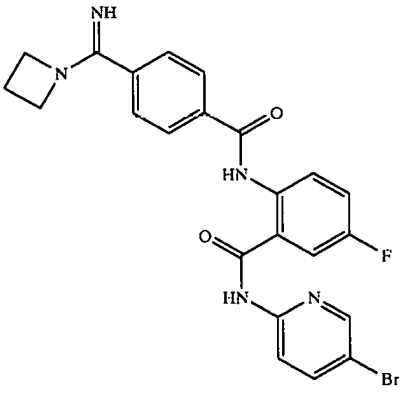
MS (M+H):482,484

Example 181



MS (M+H):470, 472

Example 184



MS (M+H):496, 498

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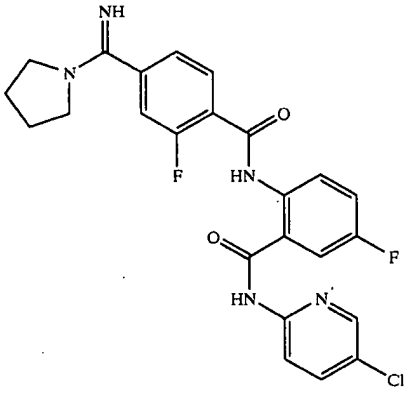
Example185



MS (M+H):484, 486

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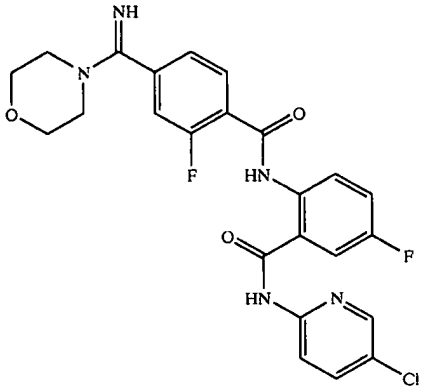
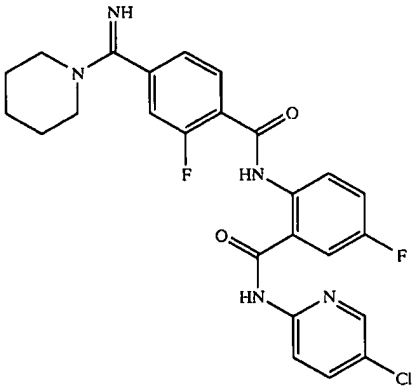
Example 188



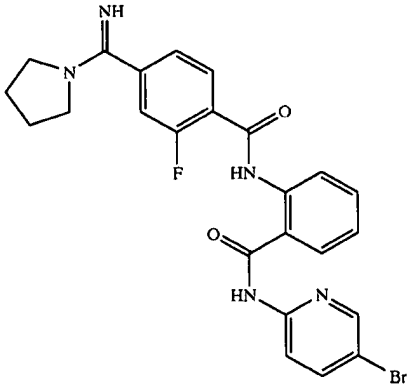
MS (M+H):500, 502

Example 186



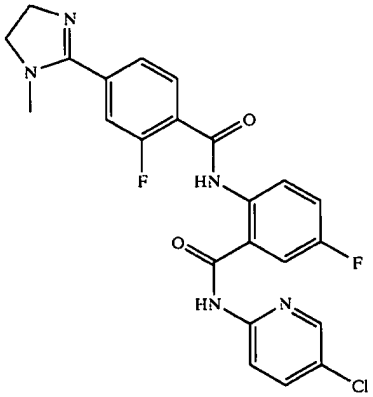
MS (M+H):498, 500

Example 189



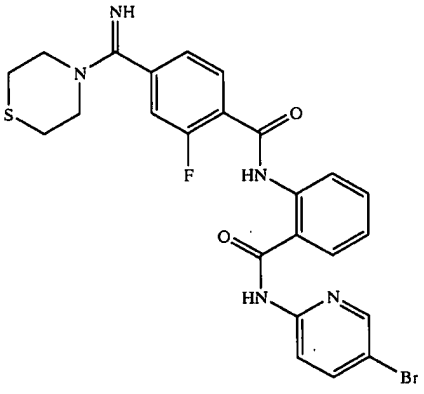
MS (M+H):510, 512

Example 187



MS (M+H):470, 472

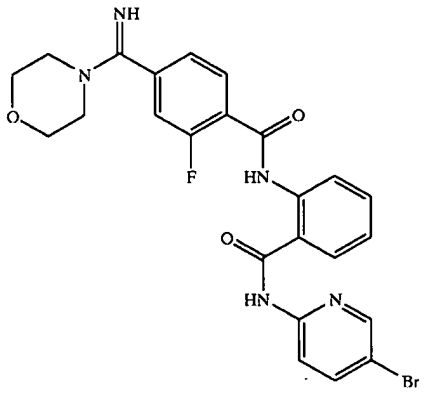
Example 190



MS (M+H):542, 544

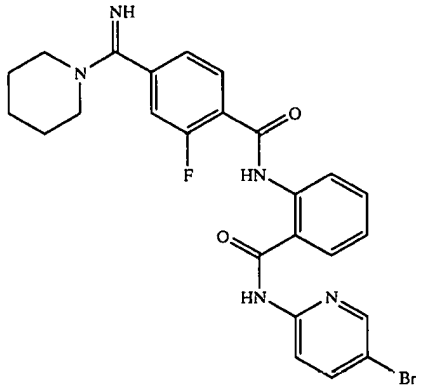
-continued

Example 191



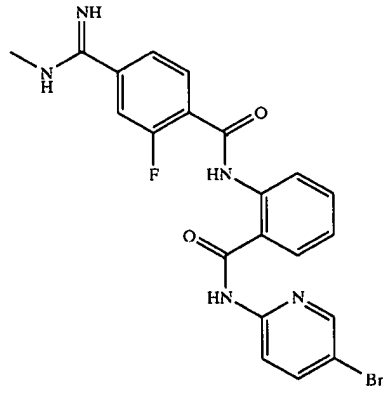
MS (M+H):526, 528

Example 192



MS (M+H):524, 526

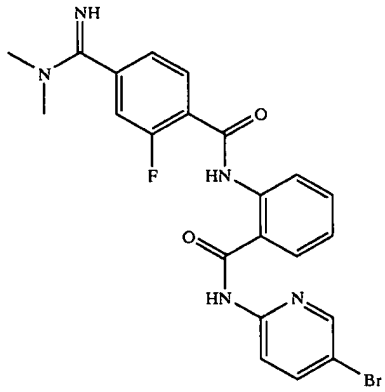
Example 193



MS (M+H):470, 472

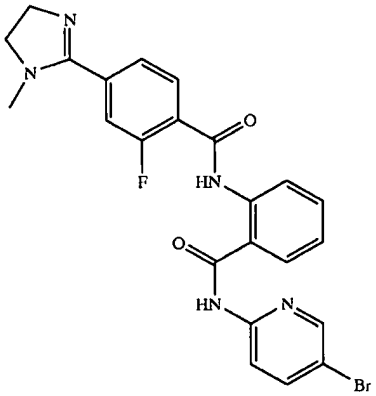
-continued

Example 194



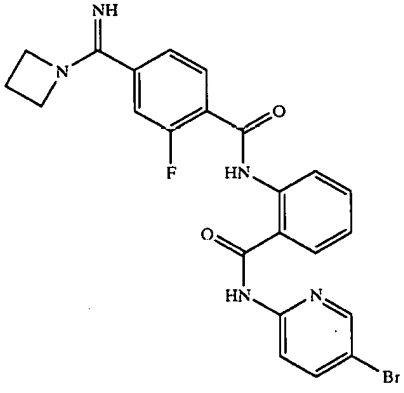
MS (M+H):484, 486

Example 195



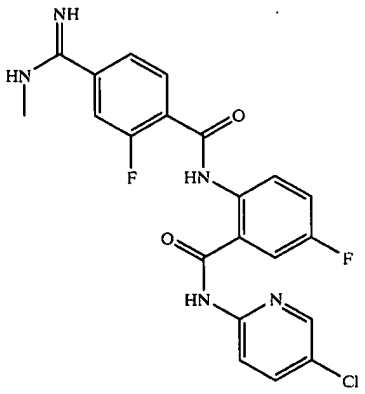
MS (M+H):496, 498

Example 196



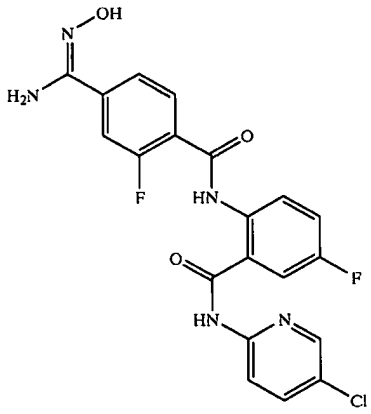
MS (M+H):496, 498

-continued



MS (M+H):444, 446

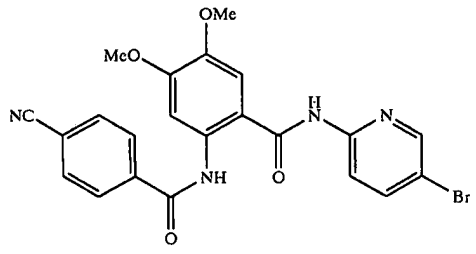
Example 198



MS (M+H):446, 448

Example 199

N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}(4-cyanophenyl)carboxamide



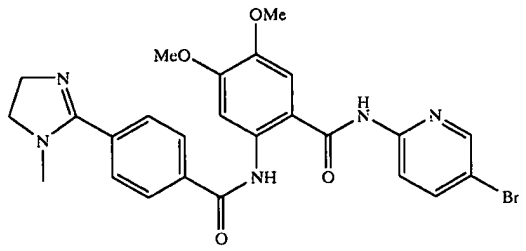
To a solution of 4,5-dimethoxy-2-nitrobenzoic acid (2.2 gm, 10 mmol) and 2-amino-5-bromopyridine (2.4 gm, 14 mmol) in anhydrous pyridine (50 mL) at 0° C. was added $POCl_3$ (1.9 mL, 20 mmol). After stirring at room temperature for 30 min, the reaction was complete. The mixture was concentrated and diluted with EtOAc (200 mL). The organic solution was washed with brine, dried and evaporated to give intermediate compound 1 (3.0 gm, 80%). MS found for $C_{14}H_{12}BrN_3O_5$ $(M+H)^+$: 382.00, 383.95.

A mixture of intermediate compound 1 (320 mg, 0.83 mmol) and $SnCl_2.2H_2O$ (900 mg, 4.0 mmol) in EtOAc (10 mL) was refluxed for 1 hour. Reduction completed. The solid was filtered through a celite bed. The filtrate was diluted with EtOAc (50 mL), and the red solution was washed with 1N aq. NaOH solution (x3) and brine, dried and evaporated to give intermediate compound 2 (230 mg, 78%). MS found for $C_{14}H_{14}BrN_3O_3$ $(M+H)^+$: 352.00, 354.05.

To a solution of intermediate compound 2 (200 mg, 0.57 mmol) in a mixture of pyridine (3 mL) and DCM (10 mL) was added 4-cyanobenzoyl chloride (140 mg, 0.85 mmol). Precipitate formed immediately and the reaction was complete. The solid was collected by filtration and washed with DCM. After drying in vacuo, the titled compound was obtained as a yellow solid in 70% yield (190 mg). MS found for $C_{22}H_{17}BrN_4O_4$ $(M+H)^+$: 481.00, 483.00.

Example 200

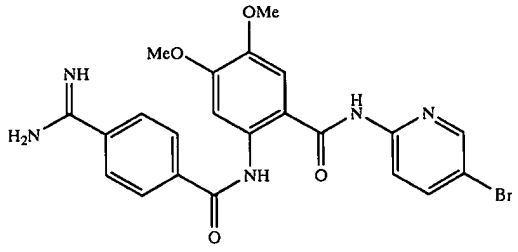
(4,5-dimethoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl]carbonylamino}phenyl)-N-(5-bromo(2-pyridyl))carboxamide



To a solution of compound obtained in Example 259 (100 mg, 0.20 mmol) in 10% Et_3N/pyridine (10 mL) at 0° C. was bubbled dry H_2S gas to saturation. The mixture was stirred at ambient temperatures overnight, and the conversion was complete. The solvent was removed to dryness, and the residue was suspended in anhydrous acetone (10 mL), followed by addition of MeI (1 mL). The reaction mixture was refluxed for 1 hour. The solvent was removed by rotary evaporation. To the residue was added anhydrous MeOH (10 mL) and N-methylethylenediamine (1 mL). The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound. MS found for $C_{25}H_{24}BrN_5O_4$ $(M+H)^+$: 538.1, 540.1.

Example 201

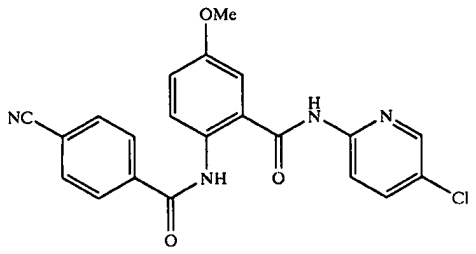
4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}carbamoyl)-benzenecarboxamidine



The title compound was obtained according to the procedure previously described. MS found for $C_{22}H_{20}BrN_5O_4$ $(M+H)^+$: 498.1, 500.0.

Example 202

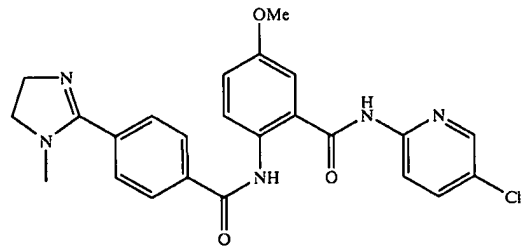
N-(5-chloro(2-pyridyl))[2-[(4-cyanophenyl) carbonylamino]-5-methoxyphenyl}-carboxamide



The title compound was obtained according to the procedure previously described.
MS found for $C_{21}H_{15}ClN_4O_3$ $(M+H)^+$: 407.0.

Example 203

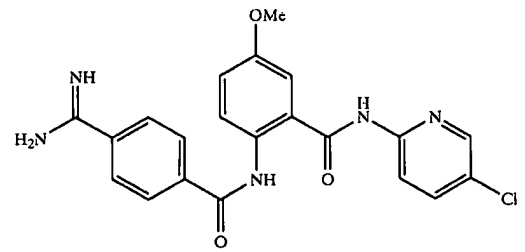
N-(5-chloro(2-pyridyl))(5-methoxy-2-{[4-(1-methyl (2-imidazolin-2-yl))phenyl]-carbonylamino}phenyl) carboxamide



To the suspension of the compound Example 262 (100 mg) in a mixture of anhydrous MeOH (5 mL) and EtOAc (5 mL) at 0° C. was bubbled anhydrous HCl gas to saturation. The mixture was stirred at ambient temperatures overnight. The conversion completed. The solvent was evaporated to dryness. The residue was dissolved in anhydrous MeOH (10 mL), followed by addition of N-methylethylenediamine (1 mL). The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound 263. MS found for $C_{24}H_{22}ClN_5O_3$ $(M+H)^+$: 464.

Example 204

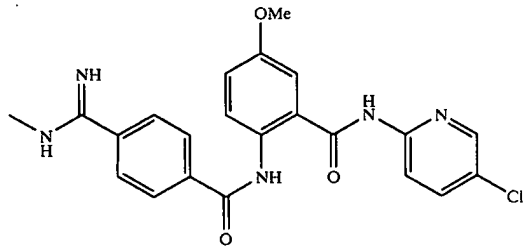
4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methoxyphenyl}carbamoyl)benzene-carboxamidine



The title compound was obtained according to the procedure previously described.
MS found for $C_{21}H_{18}ClN_5O_3$ $(M+H)^+$: 424.

Example 205

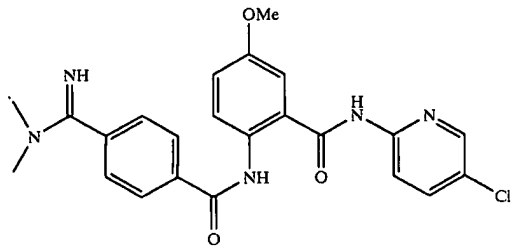
N-(5-chloro(2-pyridyl))[2-({4-[imino(methylamino) methyl]phenyl}carbonylamino)-5-methoxyphenyl] carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{22}H_{20}ClN_5O_3$ $(M+H)^+$: 438.

Example 206

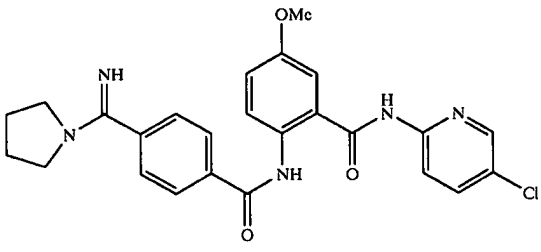
[2-({4-[(dimethylamino)iminomethyl] phenylcarbonylamino)-5-methoxyphenyl]-N-(5-chloro(2-pyridyl))carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{23}H_{22}ClN_5O_3$ $(M+H)^+$: 452.

Example 207

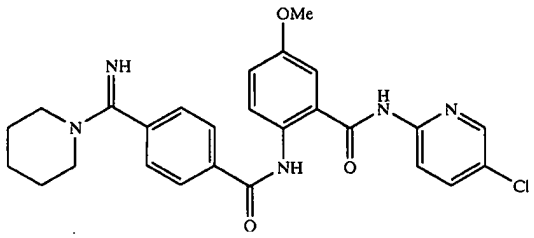
N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure previously described.
MS found for $C_{25}H_{24}ClN_5O_3$ $(M+H)^+$: 478.

Example 208

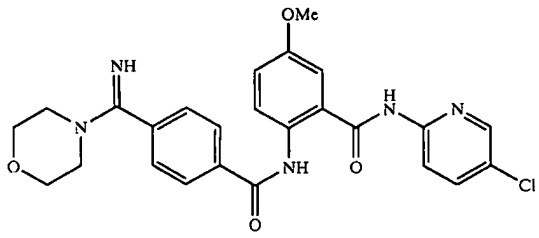
N-(5-chloro(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{26}H_{26}ClN_5O_3$ $(M+H)^+$: 492.

Example 209

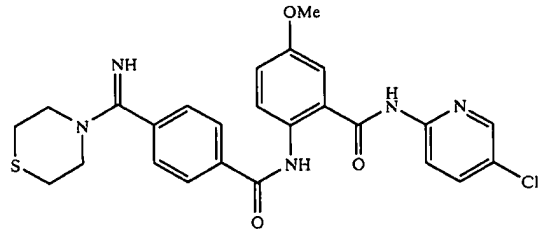
N-(5-chloro(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamin}-5-methoxyphenyl) carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{25}H_{24}ClN_5O_4$ $(M+H)^+$: 494.1.

Example 210

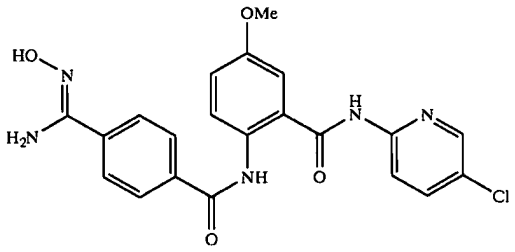
N-(5-chloro(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl] carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{25}H_{24}ClN_5O_3S$ $(M+H)^+$510.

Example 211

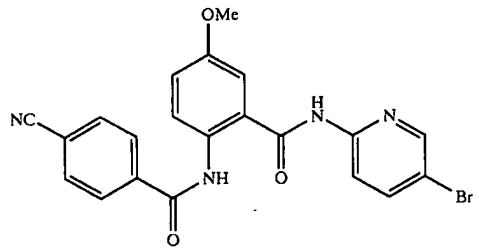
(2-{[4-(amino(hydroxyimino)methyl)phenyl] carbonylamino}-5-methoxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide



To a suspension of compound N-(5-chloro(2-pyridyl))(2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide (150 mg) in EtOH (10 mL) was added hydroxyamine hydrochloride (80 mg) and Et_3N (200 μL). The mixture was stirred at 60° C. overnight and the reaction was complete. The solvent was evaporated and the crude material was purified by RP-HPLC to give the title compound. MS found for $C_{21}H_{18}ClN_5O_4$ $(M+H)^+$: 440.1.

Example 212

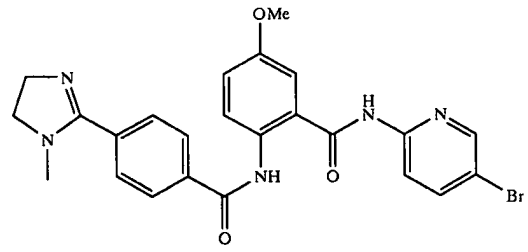
N-(5-bromo(2-pyridyl))(2-[(4-cyanophenyl) carbonylamino]-5-methoxyphenyl}carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{21}H_{15}BrN_4O_3$ $(M+H)^+$: 451.00, 453.00.

Example 213

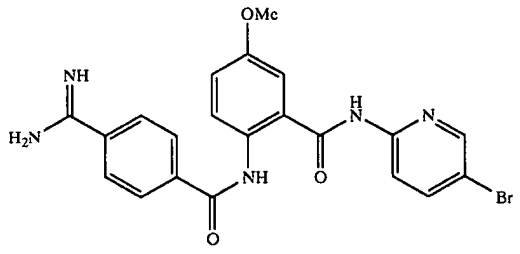
N-(5-bromo(2-pyridyl))(5-methoxy-2-{[4-(1-methyl (2-imidazolin-2-yl))phenyl]carbonylamino}phenyl) carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{24}H_{22}BrN_5O_3$ $(M+H)^+$: 508, 510.

Example 214

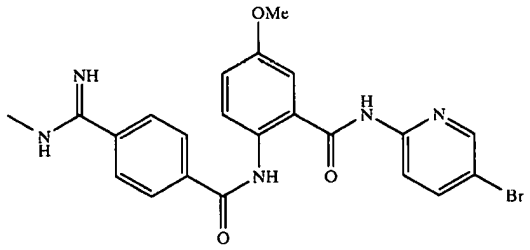
4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4-methoxyphenyl}carbamoyl)benzenecarboxamidine



The title compound was obtained according to the proccdure previously described. MS found for $C_{21}H_{18}BrN_5O_3$ $(M+H)^+$: 468.05, 470.00.

Example 215

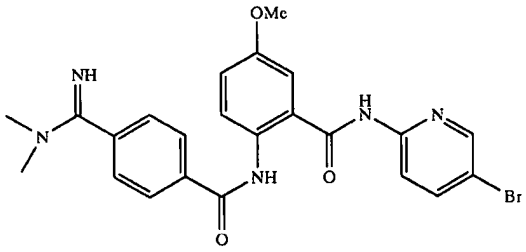
N-(5-bromo(2-pyridyl))[2-({4-[imino(methylamino)methyl]phenyl}carbonylamino)-5-methoxyphenyl]carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{22}H_{20}BrN_5O_3$ $(M+H)^+$: 482, 484.

Example 216

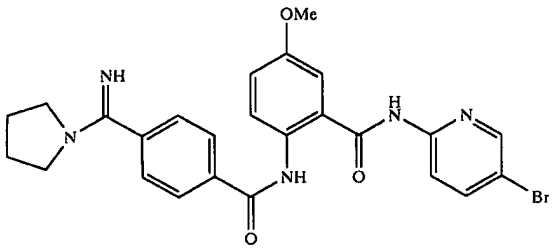
[2-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-bromo(2-pyridyl))carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{23}H_{22}BrN_5O_3$ $(M+H)^+$: 496.1, 498.1.

Example 217

N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

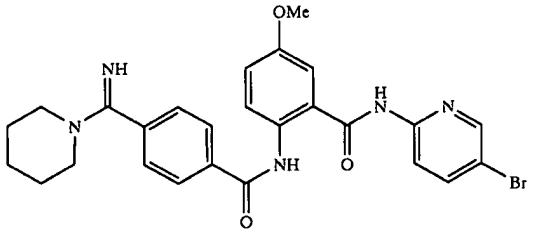


The title compound was obtained according to the procedure previously described.

MS found for $C_{25}H_{24}BrN_5O_3$ $(M+H)^+$: 522, 524.

Example 218

N-(N-(5-bromo(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyplhenyl)carboxamide

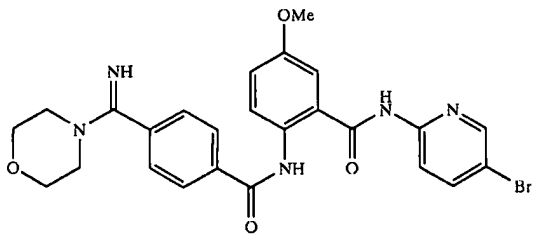


The title compound was obtained according to the procedure previously described.

MS found for $C_{26}H_{26}BrN_5O_3$ $(M+H)^+$: 536.1, 538.1.

Example 219

N-(5-bromo(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide

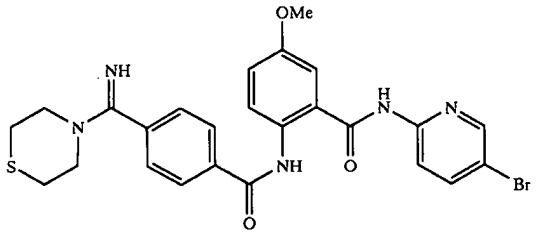


The title compound was obtained according to the procedure previously described.

MS found for $C_{25}H_{24}BrN_5O_4$ $(M+H)^+$: 538.1, 540.1.

Example 220

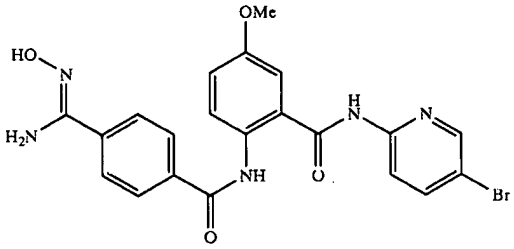
N-(5-bromo(2-pyridyl))(2-{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide



The title compound was obtained according to the procedure previously described.
MS found for $C_{25}H_{24}BrN_5O_3S$ (M+H)$^+$: 554.1, 556.05.

Example 221

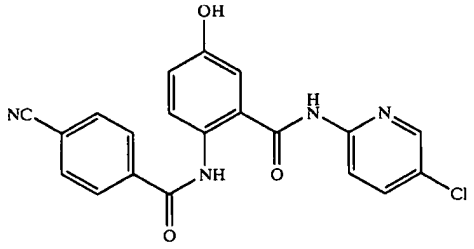
(2-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide



The title compound was obtained according to the procedure previously described.
MS found for $C_{21}H_{18}BrN_5O_4$ (M+H)$^+$: 484.1, 486.0.

Example 222

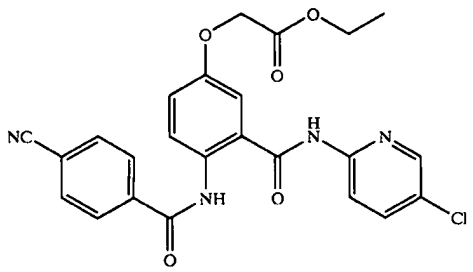
N-(5-chloro(2-pyridyl))(6-[(4-cyanophenyl)carbonylamino]-3-hydroxyphenyl}carboxamide



To a suspension of compound N-(5-chloro(2-pyridyl))(2-[(4-cyanophenyl)-carbonylamino]-5-methoxyphenyl}carboxamide (500 mg, 1.2 mmol) in DCM (100 mL) at −78° C. was added BBr_3 (2 mL). The mixture was stirred at ambient temperatures for 72 hours. The solid was collected by filtration and was washed by DCM and water, dried under vacuum. The filtrate was concentrated and extracted with EtOAc. The organic extract was washed with brine, dried and evaporated. The resulting solid was combined with the solid obtained from filtration to give the title compound. Total yield is 90% (430 mg). MS found for $C_{20}H_{13}ClN_4O_3$ (M+H)$^+$: 393.0.

Example 223

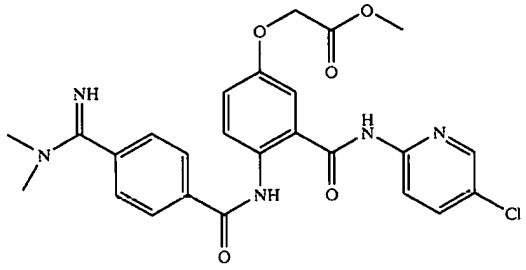
methyl2-{3-[N-(5-chloro(2-pyridyl))carbamoyl]-4-[(4-cyanophenyl)carbonylamino]-phenoxy}acetate



To a mixture of compound N-(5-chloro(2-pyridyl))(6-[(4-cyanophenyl)-carbonylamino]-3-hydroxyphenyl}carboxamide (50 mg, 0.13 mmol) and Cs_2CO_3 (83 mg, 0.25 mmol) in DMF (1 mL) at room temperature was added ethyl bromoacetate (15 μL, 0.13 mmol). The mixture was stirred for 1 hour before diluted with EtOAc (20 mL) and water (10 mL). The organic layer was washed with brine dried and evaporated to give 70 mg of the crude compound, which was used without farther purification. MS found for $C_{24}H_{19}ClN_4O_5$ (M+H)$^+$: 479.0.

Example 224

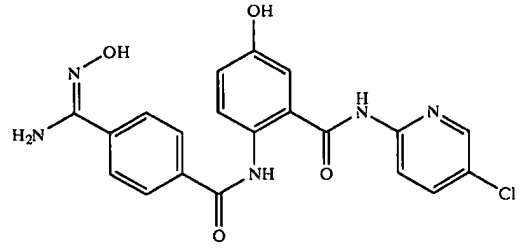
methyl 2-[4-({4-[(dimethylamino)iminomethyl]phenyl}carbonylamino)-3-[N-(5-chloro(2-pyridyl))carbamoyl]phenoxy]acetate



The title compound was obtained according to the procedure previously described. MS found for $C_{25}H_{24}ClN_5O_5$ (M+H)$^+$: 510.1.

Example 225

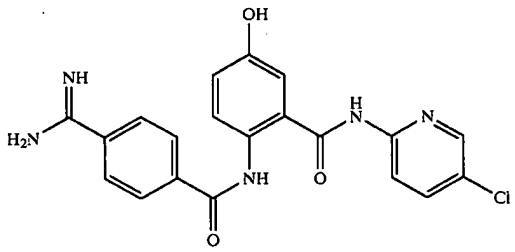
(6-{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-3-hydroxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide



The title compound was obtained according to the procedure previously described. MS found for $C_{20}H_{16}ClN_5O_4$ (M+Na)$^+$: 448.0.

Example 226

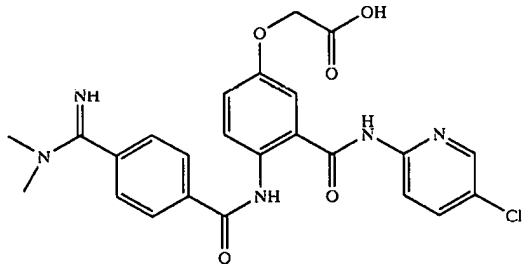
4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]4-hydroxyphenyl}carbamoyl)-benzenecarboxamidine



The title compound was obtained according to the procedure previously described. MS found for $C_{20}H_{16}ClN_5O_3$ $(M+H)^+$: 410.1.

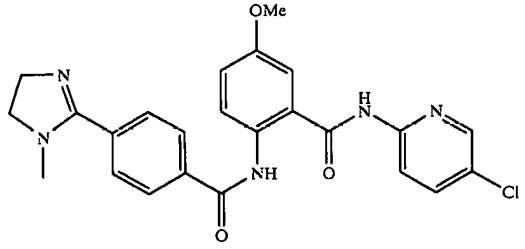
Example 227

4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-hydroxyphenyl}carbamoyl)-benzenecarboxamidine



To a solution of Example 284 (10 mg) in MeOH (1 mL) was added 50 μL of 1N aq. LiOH solution. The mixture was stirred for 1 hour and purified by RP-HPLC to give the title compound. MS found for $C_{24}H_{22}ClN_5O_5$ $(M+H)^+$: 496.

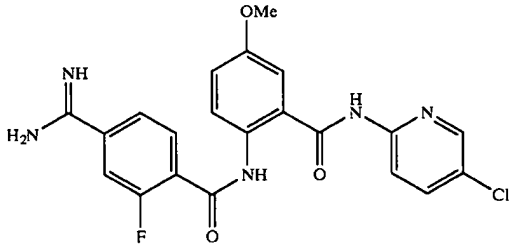
Example 228



$C_{24}H_{21}ClFN_5O_3$
Exact Mass: 481.13
Mol. Wt.: 481.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{21}ClFN_5O_3$: $(M+H)^+$: 482.1.

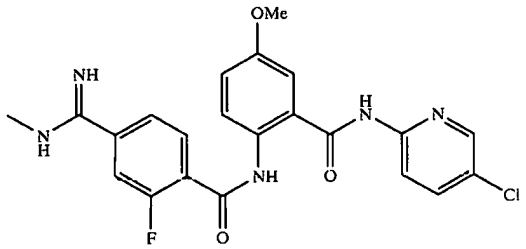
Example 229



$C_{21}H_{17}ClFN_5O_3$
Exact Mass: 441.10
Mol. Wt.: 441.84

The title compound was synthesized according to the procedure described previously. MS found for $C_{21}H_{17}ClFN_5O_3$: $(M+H)^+$: 442.1.

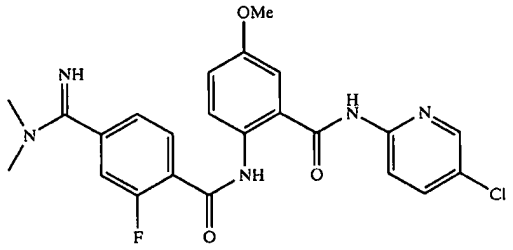
Example 230



$C_{22}H_{19}ClFN_5O_3$
Exact Mass: 455.12
Mol. Wt.: 455.87

The title compound was synthesized according to the procedure described previously. MS found for $C_{22}H_{19}ClFN_5O_3$: $(M+H)^+$: 456.1.

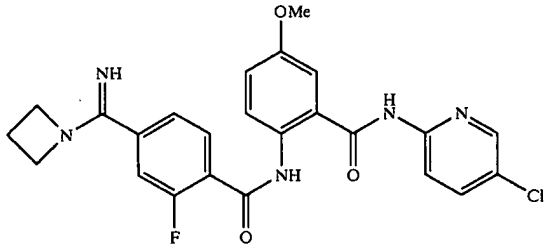
Example 231



$C_{23}H_{21}ClFN_5O_3$
Exact Mass: 469.13
Mol. Wt.: 469.90

The title compound was synthesized according to the procedure described previously. MS found for $C_{23}H_{21}ClFN_5O_3$: $(M+H)^+$: 470.1.

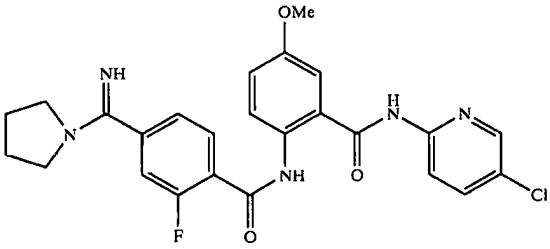
Example 232



$C_{24}H_{21}ClFN_5O_3$
Exact Mass: 481.13
Mol. Wt.: 481.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{21}ClFN_5O_3$: $(M+H)^+$: 482.1.

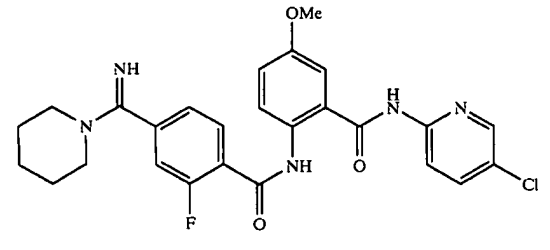
Example 233



$C_{25}H_{23}ClFN_5O_3$
Exact Mass: 495.15
Mol. Wt.: 495.93

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{23}ClFN_5O_3$: $(M+H)^+$: 496.1.

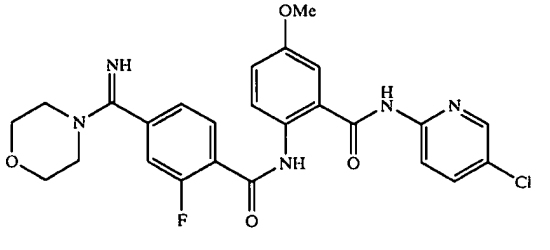
Example 234



$C_{26}H_{25}ClFN_5O_3$
Exact Mass: 509.16
Mol. Wt.: 509.96

The title compound was synthesized according to the procedure described previously. MS found for $C_{26}H_{25}ClFN_5O_3$: $(M+H)^+$: 510.2.

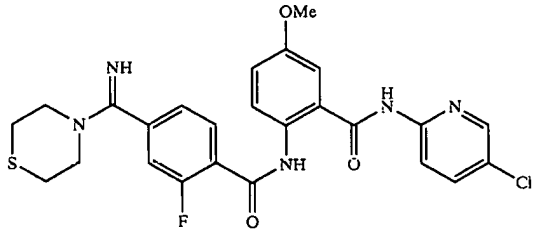
Example 235



$C_{25}H_{23}ClFN_5O_4$
Exact Mass: 511.14
Mol. Wt.: 511.93

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{23}ClFN_5O_4$: $(M+H)^+$: 512.2.

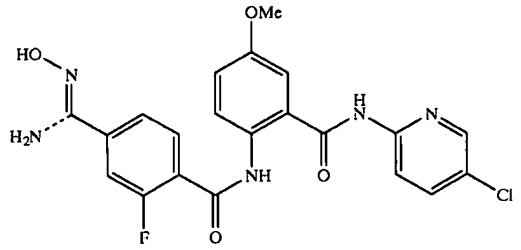
Example 236



$C_{25}H_{23}ClFN_5O_3S$
Exact Mass: 527.12
Mol. Wt.: 528.00

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{23}ClFN_5O_3S$: $(M+H)^+$: 528.1.

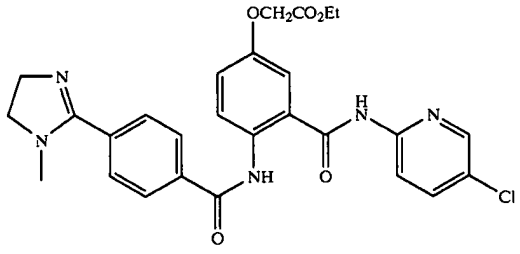
Example 237



$C_{21}H_{17}ClFN_5O_4$
Exact Mass: 457.10
Mol. Wt.: 457.84

The title compound was synthesized according to the procedure described previously. MS found for $C_{21}H_{17}ClFN_5O_4$: $(M+H)^+$: 458.1.

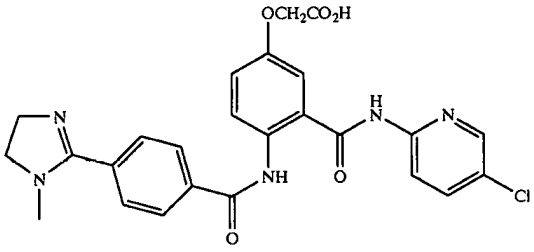
Example 238



$C_{27}H_{26}ClN_5O_5$
Exact Mass: 535.16
Mol. Wt.: 535.98

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

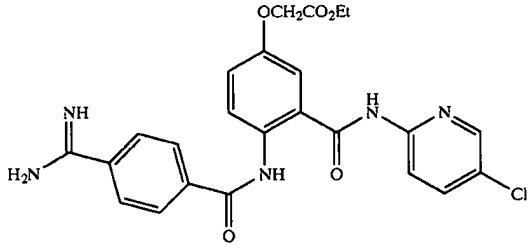
Example 239



$C_{25}H_{22}ClN_5O_5$
Exact Mass: 507.13
Mol. Wt.: 507.93

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{22}ClN_5O_5$: $(M+H)^+$: 508.1.

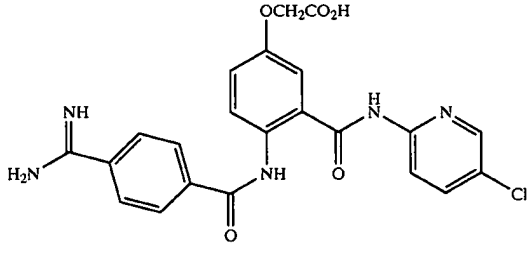
Example 240



$C_{24}H_{22}ClN_5O_5$
Exact Mass: 495.13
Mol. Wt.: 495.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{22}ClN_5O_5$: $(M+H)^+$: 496.1.

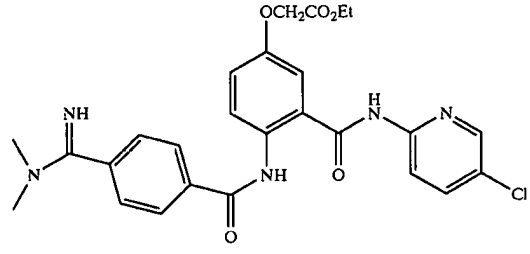
Example 241



$C_{22}H_{18}ClN_5O_5$
Exact Mass: 467.10
Mol. Wt.: 467.86

The title compound was synthesized according to the procedure described previously. MS found for $C_{22}H18ClN_5O_5$: $(M+H)^+$: 468.1.

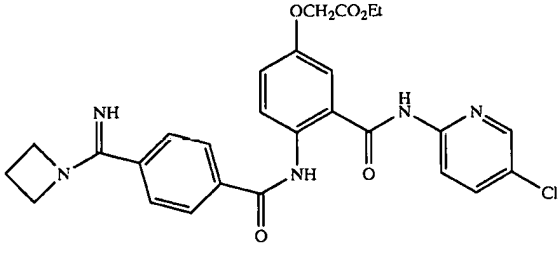
Example 242



$C_{26}H_{26}ClN_5O_5$
Exact Mass: 523.16
Mol. Wt.: 523.97

The title compound was synthesized according to the procedure described previously. MS found for $C_{26}H_{26}ClN_5O_5$: $(M+H)^+$: 524.2.

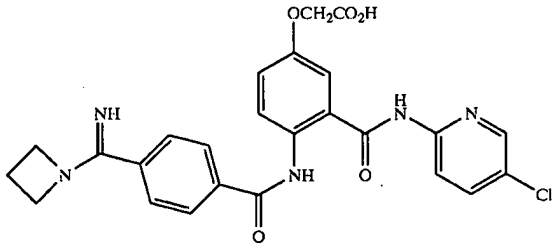
Example 243



$C_{27}H_{26}ClN_5O_5$
Exact Mass: 535.16
Mol. Wt.: 535.98

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

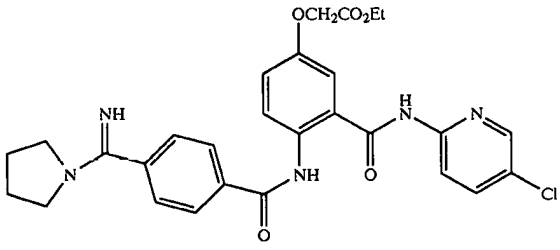
Example 244



$C_{25}H_{22}ClN_5O_5$
Exact Mass: 507.13
Mol. Wt.: 507.93

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{22}ClN_5O_5$: $(M+H)^+$: 508.1.

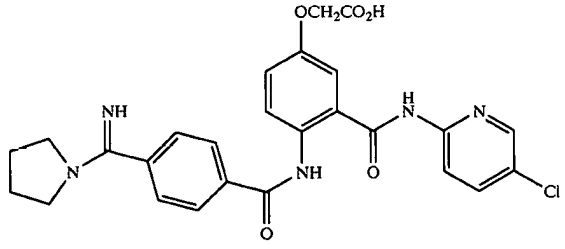
Example 245



$C_{28}H_{28}ClN_5O_5$
Exact Mass: 549.18
Mol. Wt.: 550.01

The title compound was synthesized according to the procedure described previously. MS found for $C_{28}H_{28}ClN_5O_5$: $(M+H)^+$: 550.2.

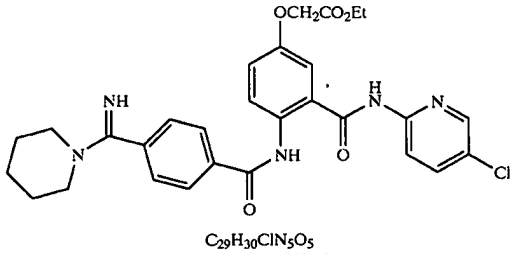
Example 246



$C_{26}H_{24}ClN_5O_5$
Exact Mass: 521.15
Mol. Wt.: 521.95

The title compound was synthesized according to the procedure described previously. MS found for $C_{26}H_{24}ClN_5O_5$: $(M+H)^+$: 522.1.

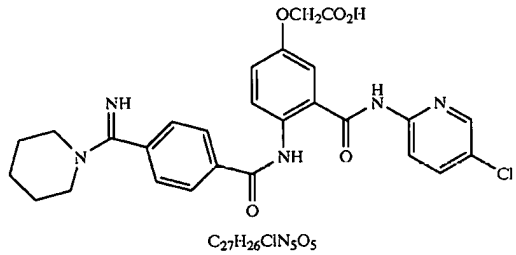
Example 247



$C_{29}H_{30}ClN_5O_5$
Exact Mass: 563.19
Mol. Wt.: 564.03

The title compound was synthesized according to the procedure described previously. MS found for $C_{29}H_{30}ClN_5O_5$: $(M+H)^+$: 564.2.

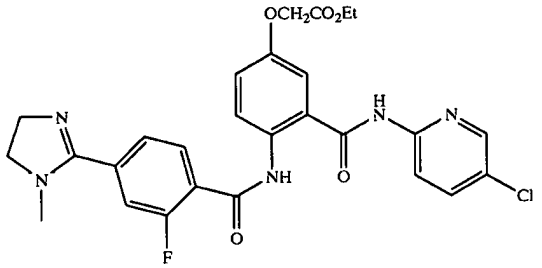
Example 248



$C_{27}H_{26}ClN_5O_5$
Exact Mass: 535.16
Mol. Wt.: 535.98

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{26}ClN_5O_5$: $(M+H)^+$: 536.1.

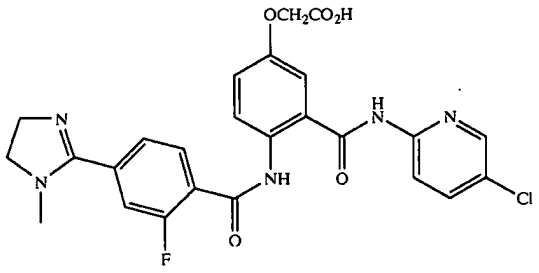
Example 249



$C_{27}H_{25}ClFN_5O_5$
Exact Mass: 553.15
Mol. Wt.: 553.97

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{25}ClFN_5O_5$: $(M+H)^+$: 554.2.

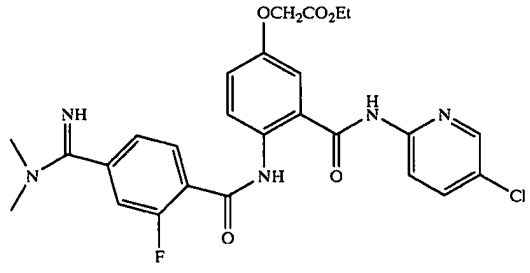
Example 250



$C_{25}H_{21}ClFN_5O_5$
Exact Mass: 525.12
Mol. Wt.: 525.92

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{21}ClFN_5O_5$: $(M+H)^+$: 526.1.

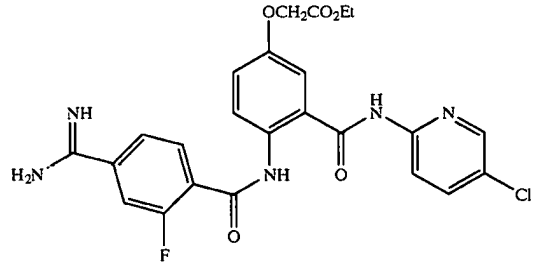
Example 253



$C_{26}H_{25}ClFN_5O_5$
Exact Mass: 541.15
Mol. Wt.: 541.96

The title compound was synthesized according to the procedure described previously. MS found for $C_{26}H_{25}ClFN_5O_5$: $(M+H)^+$: 542.1.

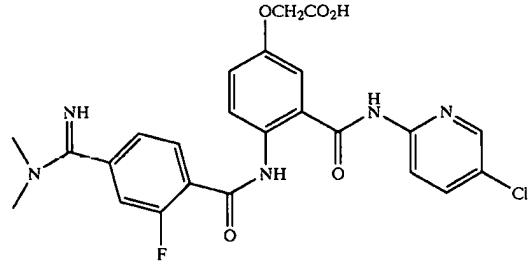
Example 251



$C_{24}H_{21}ClFN_5O_5$
Exact Mass: 513.12
Mol. Wt.: 513.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{21}ClFN_5O_5$: $(M+H)^+$: 514.1.

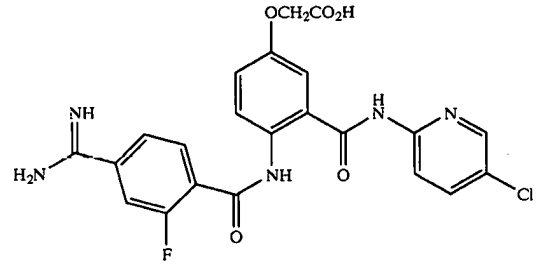
Example 254



$C_{24}H_{21}ClFN_5O_5$
Exact Mass: 513.12
Mol. Wt.: 513.91

The title compound was synthesized according to the procedure described previously. MS found for $C_{24}H_{21}ClFN_5O_5$: $(M+H)^+$: 514.1.

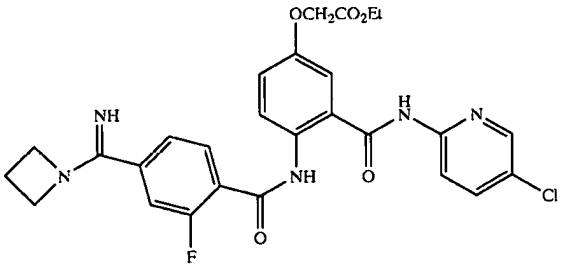
Example 252



$C_{22}H_{17}ClFN_5O_5$
Exact Mass: 485.09
Mol. Wt.: 485.85

The title compound was synthesized according to the procedure described previously. MS found for $C_{22}H_{17}ClFN_5O_5$: $(M+H)^+$: 486.

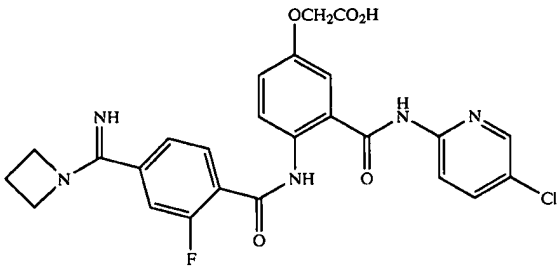
Example 255



$C_{27}H_{25}ClFN_5O_5$
Exact Mass: 553.15
Mol. Wt.: 553.97

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{25}ClFN_5O_5$: $(M+H)^+$: 554.1.

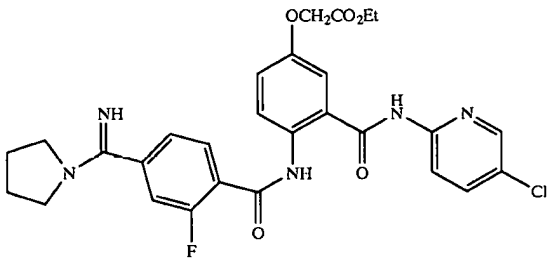
Example 256



$C_{25}H_{21}ClFN_5O_5$
Exact Mass: 525.12
Mol. Wt.: 525.92

The title compound was synthesized according to the procedure described previously. MS found for $C_{25}H_{21}ClFN_5O_5$: $(M+H)^+$: 526.1.

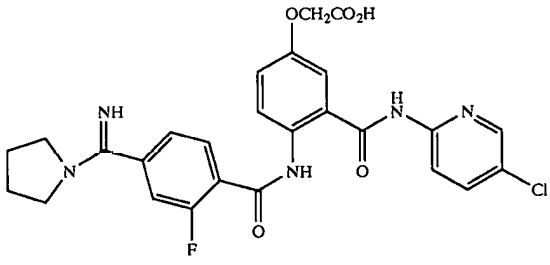
Example 257



$C_{28}H_{27}ClFN_5O_5$
Exact Mass: 567.17
Mol. Wt.: 568.00

The title compound was synthesized according to the procedure described previously. MS found for $C_{28}H_{27}ClFN_5O_5$: $(M+H)^+$: 568.1.

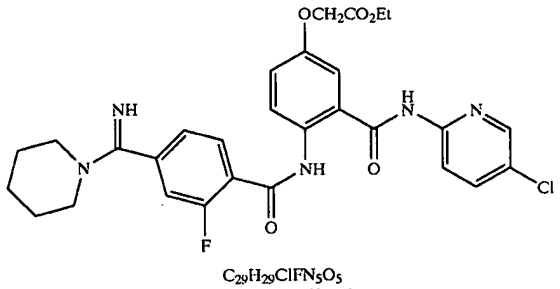
Example 258



$C_{26}H_{23}ClFN_5O_5$
Exact Mass: 539.14
Mol. Wt.: 539.94

The title compound was synthesized according to the procedure described previously. MS found for $C_{26}H_{23}ClFN_5O_5$: $(M+H)^+$: 540.1.

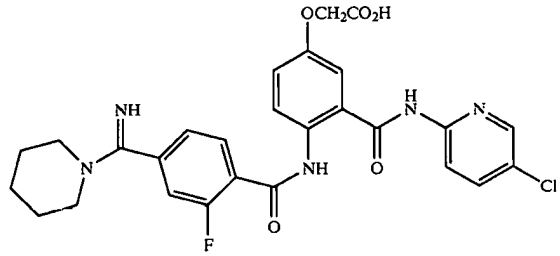
Example 259



$C_{29}H_{29}ClFN_5O_5$
Exact Mass: 581.18
Mol. Wt.: 582.02

The title compound was synthesized according to the procedure described previously. MS found for $C_{29}H_{29}ClFN_5O_5$: $(M+H)^+$: 582.2.

Example 260

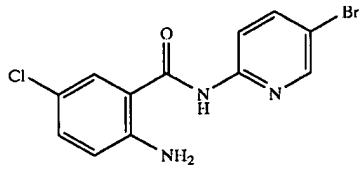


$C_{27}H_{25}ClFN_5O_5$
Exact Mass: 553.15
Mol. Wt.: 553.97

The title compound was synthesized according to the procedure described previously. MS found for $C_{27}H_{25}ClN_5O_5$: $(M+H)^+$: 554.1.

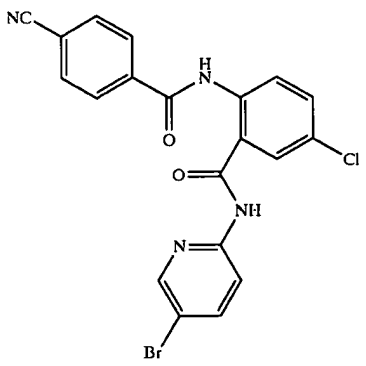
Example 261

Step 1:



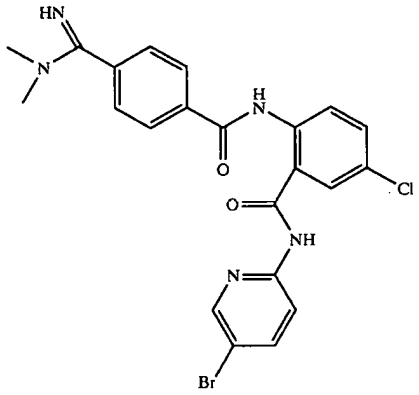
To a solution of 2-amino-5-bromopyridine (882 mg, 5.1 mmol) in tetrahydrofuran (5 ml) was added 0.5M potassium bis(trimethylsilyl)amide in toluene (20 ml, 10.1 mmol) dropwise at −78° C. After stirred for additional 0.5 hr at −78° C., the mixture was added 5-chloroisatoic anhydride (1 g, 5.1 mmol) at −78° C. The mixture was warmed up to r.t gradually and stirred overnight. After concentrated, the crude was washed with saturated ammonium chloride solution and extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-bromophenyl)-N-(5-chloro(2-pyridyl)) carboxamide as yellow solid (1.54 g. 92%). MS found for C12H9BrClN3O M^+=327, $(M+2)^+$=329.

Step 2:



To a solution of the compound of (2-amino-5-bromophenyl)-N-(5-chloro(2-pyridyl))carboxamide (1.33 g, 4.07 mmol) in dichloromethane (10 ml) was added 4-cyanobenzoly chloride (808 mg, 4.88 mmol) and pyridine (1 ml, 12.21 mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with a little amount of dichloromethane to give N-{4-chloro-2-[N-(5-bromo(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide as yellow solid (1.36 g, 73%). MS found for C20H12BrClN4O2 M^+=455, $(M+2)^+$=457.

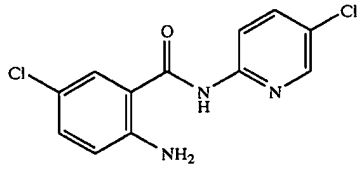
Step 3:



To a solution of the compound of N-{4-chloro-2-[N-(5-bromo(2-pyridyl))carbamoyl]phenyl (4-cyanophenyl) carboxamide (1.36 g, 3 mmol) in anhydrous pyridine (20 ml) and triethyl amine (2 ml) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at r.t. overnight. After concentrated, the residue was dissolved in anhydrous acetone (20 ml) and iodomethane (1.87 ml, 30 mmol) was added. The mixture was refluxed for 2 hrs. After concentrated, the residue was dissolved in anhydrous methanol (20 ml) and a solution of 2M dimethylamine (in THF) (15 ml, 30 mmol) and acetic acid (10 ml) in anhydrous methanol (5 ml) was added. The mixture was refluxed for 2 hrs. After concentrated, the crude residue was purified by RP-HPLC to give target as white solid (750 mg, 50%). MS found C22H19BrClN5O2 M^+=500, $(M+2)^+$=502.

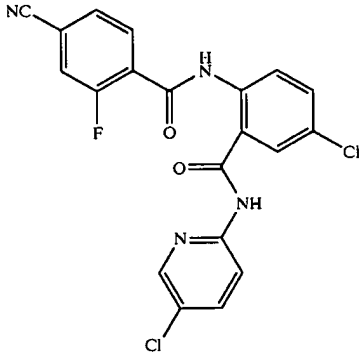
Example 262

Step 1:



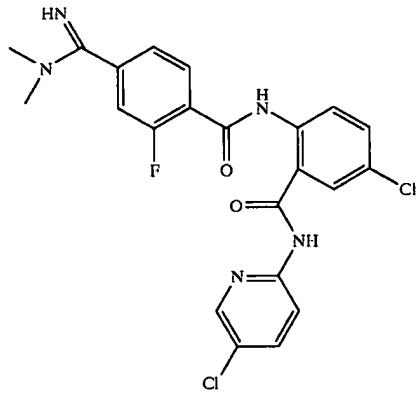
To a solution of 2-amino-5-chloropyridine (787 mg, 6.1 mmol) in tetrahydrofuran (5 ml) was added 0.5M potassium bis(trimethylsilyl)amide in toluene (20 ml, 10.1 mmol) dropwise at −78° C. After stirred for additional 0.5 hr at −78° C., the mixture was added 5-chloroisatoic anhydride (1 g, 5.1 mmol) at −78° C. The mixture was warmed up to r.t gradually and stirred overnight. After concentrated, the crude was washed with saturated ammonium chloride solution and extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl)) carboxamide as yellow solid (1.39 g. 99%). MS found for C12H9Cl2N3O M^+=282, $(M+2)^+$=284.

Step 2:



A solution of 2-fluoro-4-cyanobenzoic acid (1 g, 6.06 mmol) in thionyl chloride (5 ml) was refluxed for 2 hr. After concentration, the residue was dissolved in dichloromethane (5 ml). And a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (1.2 g, 4.25 mmol). in dichloromethane (10 ml) and pyridine (1.47 ml, 18.18 mmol) were added. The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with a little amount of dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(2-fluoro-4-cyanophenyl)carboxamide (2.03 g, 78%). MS found for C20H11C12FN4O2 M^+=429, $(M+2)^+$=431.

Step 3:

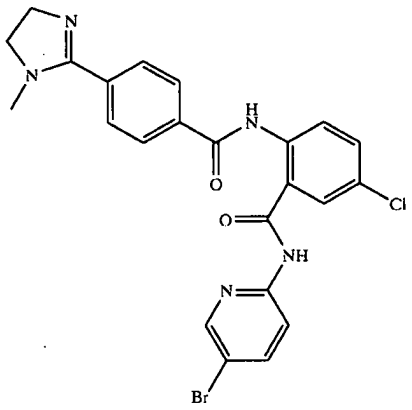


To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(2-fluoro-4-cyanophenyl)carboxamide (3 g, 7 mmol) in anhydrous pyridine (40 ml) and triethyl amine (4 ml) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at r.t. overnight. After concentrated, the residue was dissolved in anhydrous acetone (60 ml) and iodomethane (4.36 ml, 70 mmol) was added. The mixture was refluxed for 2 hrs. After concentrated, the residue was dissolved in anhydrous methanol (50 ml) and a solution of 2M dimethylamine (in THF) (35 ml, 70 mmol) and acetic acid (30 ml) in anhydrous methanol (15 ml) was added. The mixture was refluxed for 2 hrs. After concentrated, the crude residue was purified by RP-HPLC to give target as white solid (1.7 g, 50%). MS found C22H18Cl2FN5O2 M^+=474, $(M+2)^+$=476.

Examples 263–280

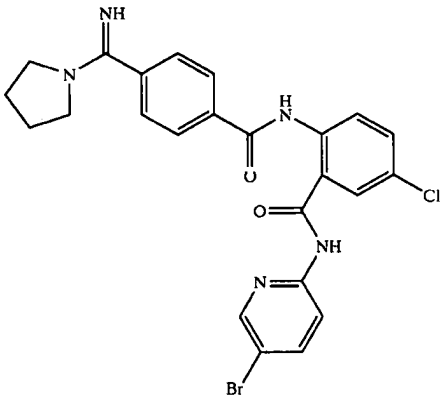
The following compounds were similarly prepared.

Example 263



M+ = 512
(M+2)+ = 514
$C_{23}H_{19}BrClN_5O_2$

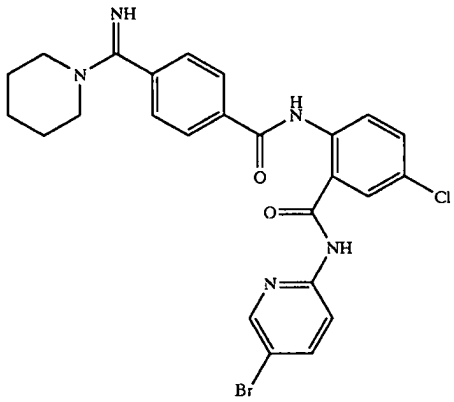
Example 264



M^+ = 526
(M+2)+ = 528
$C_{24}H_{21}BrClN_5O_2$

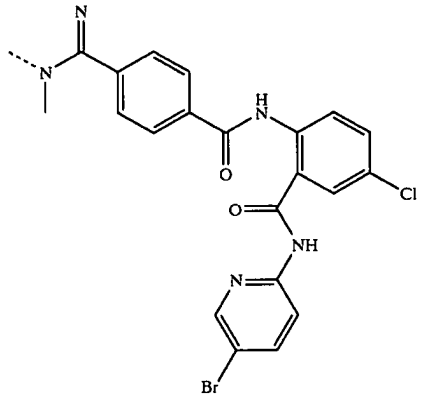
-continued

Example 265



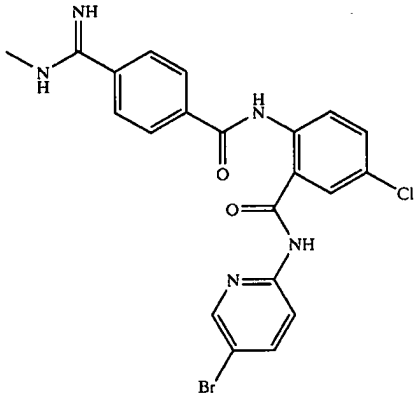
M^+ = 540
$(M+2)^+$ = 542
$C_{25}H_{23}BrClN_5O_2$

Example 266



M^+ = 500
$(M+2)^+$ = 502
$C_{22}H_{19}BrClN_5O_2$

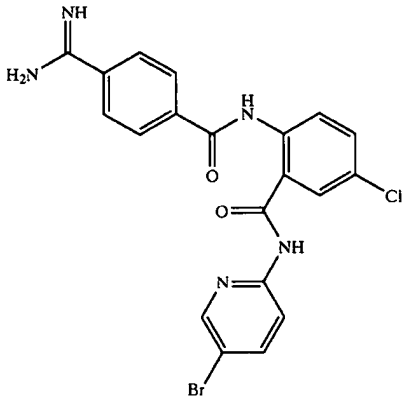
Example 267



M^+ = 486
$(M+2)^+$ = 488
$C_{21}H_{17}BrClN_5O_2$

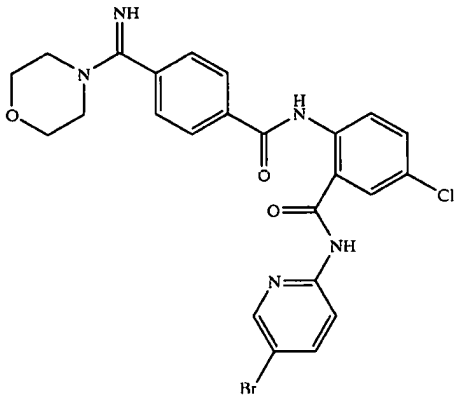
-continued

Example 268



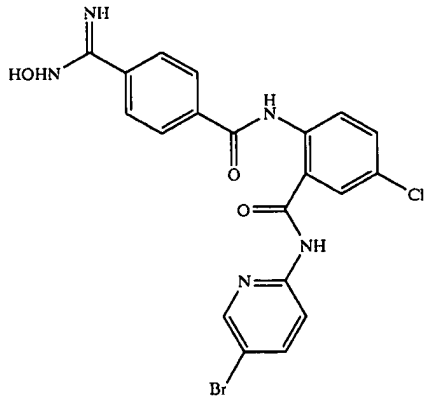
$M^+ = 472$
$(M+2)^+ = 474$
$C_{20}H_{15}BrClN_5O_2$

Example 269



$M^+ = 542$
$(M+2)^+ = 544$
$C_{24}H_{21}BrClN_5O_3$

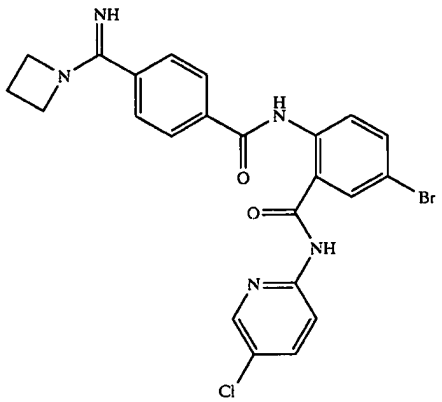
Example 270



$M^+ = 488$
$(M+2)^+ = 490$
$C_{20}H_{15}BrClN_5O_3$

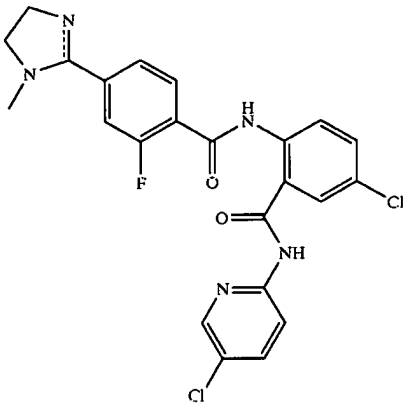
-continued

Example 271



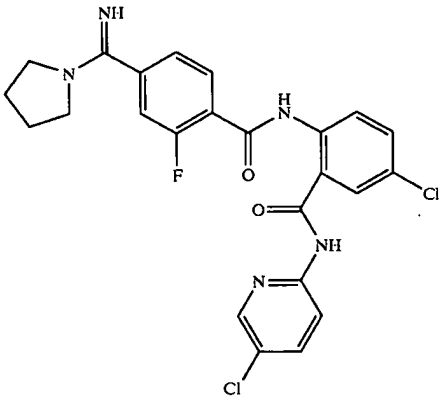
$M^+ = 512$
$(M+2)^+ = 514$
$C_{23}H_{19}BrClN_5O_2$

Example 272



M+ = 486
(M+2)+ = 488
$C_{23}H_{18}Cl_2FN_5O_2$

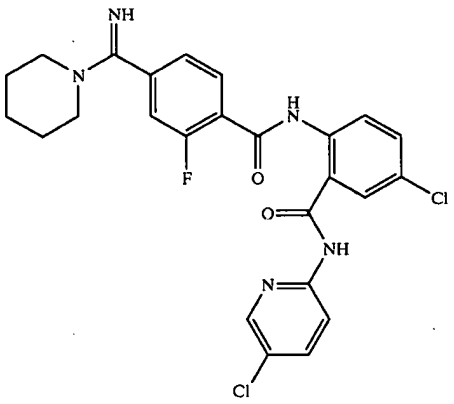
Example 273



$M^+ = 500$
(M+2)+ = 502
$C_{24}H_{20}Cl_2FN_5O_2$

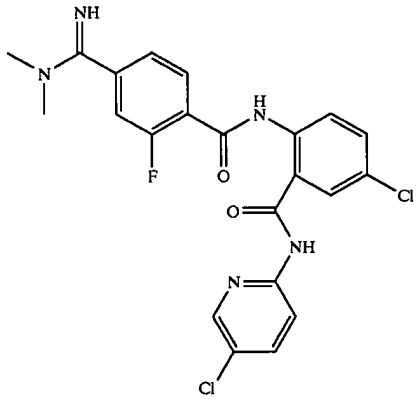
-continued

Example 274



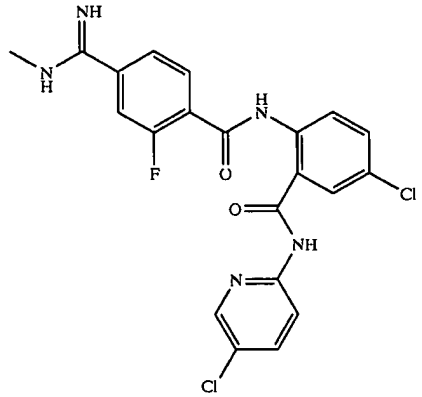
$M^+ = 514$
$(M+2)^+ = 516$
$C_{25}H_{22}Cl_2FN_5O_2$

Example 275



$M^+ = 474$
$(M+2)+ = 476$
$C_{22}H_{18}Cl_2FN_5O_2$

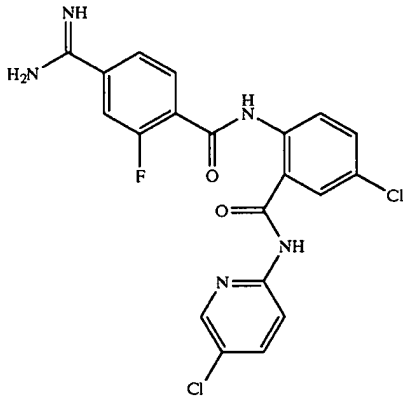
Example 276



$M^+ = 460$
$(M+2)^+ = 462$
$C_{21}H_{16}Cl_2FN_5O_2$

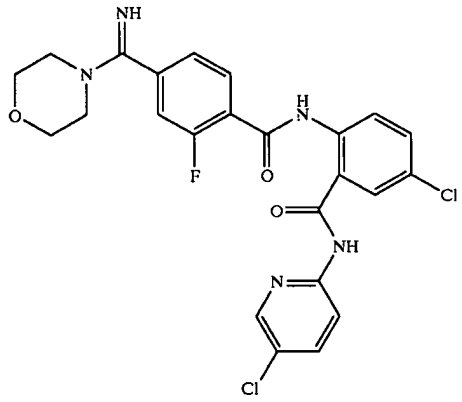
-continued

Example 277



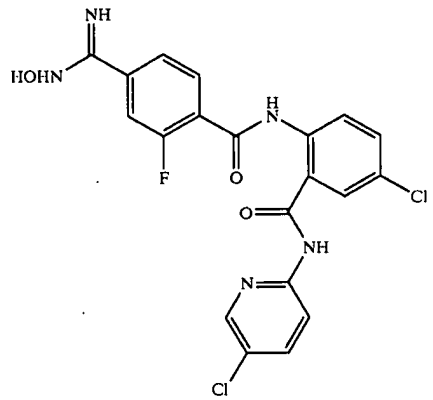
$M^+ = 446$
$(M+2)^+ = 448$
$C_{20}H_{14}Cl_2FN_5O_2$

Example 278



$M^+ = 516$
$(M+2)^+ = 518$
$C_{24}H_{20}Cl_2FN_5O_3$

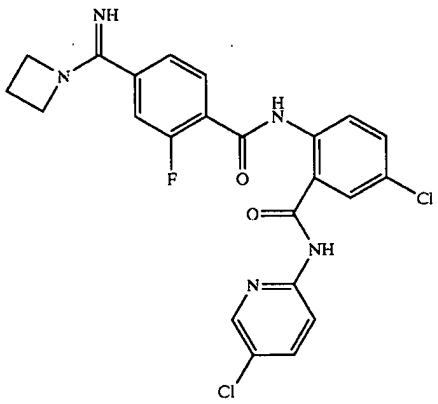
Example 279



$M^+ = 462$
$(M+2)^+ = 464$
$C_{20}H_{14}Cl_2FN_5O_3$

-continued

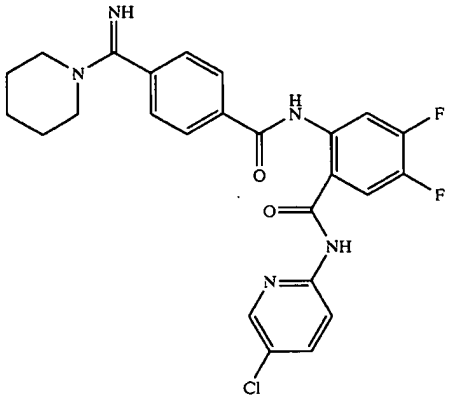
Example 280



$M^+ = 486$
$(M+2)^+ = 488$
$C_{23}H_{18}Cl_2FN_5O_2$

-continued

Example 283

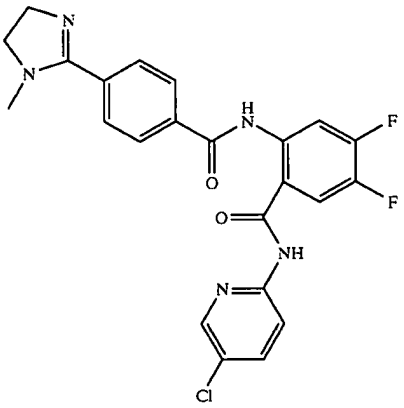


MS (M+H):496

Examples 281–287

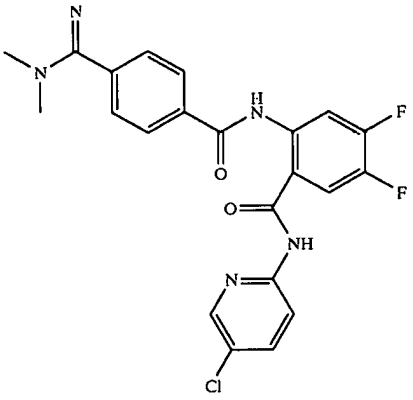
The following compounds were similarly prepared.

Example 281



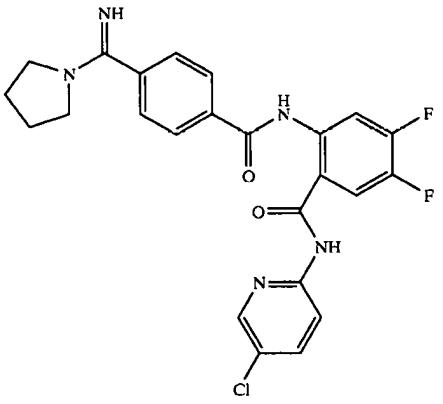
MS (M+H):470

Example 284



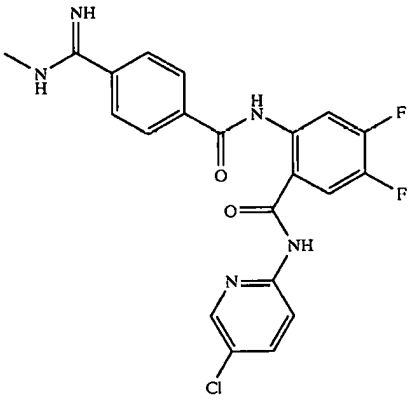
MS (M+H):458

Example 282



MS (M+H):484

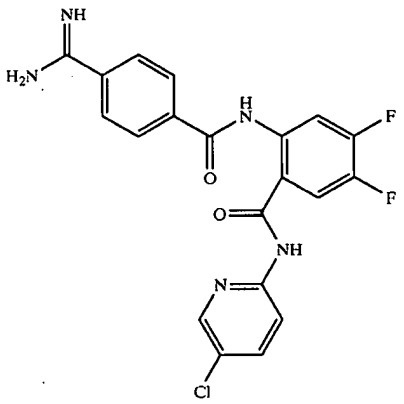
Example 285



MS (M+H):444

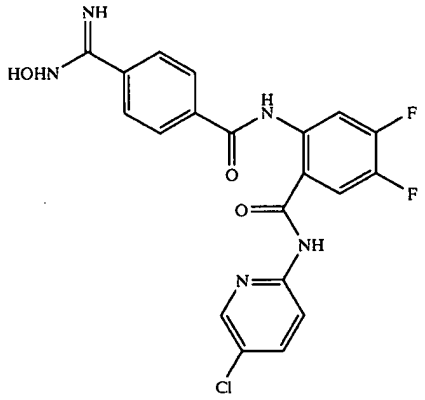
-continued

Example 286



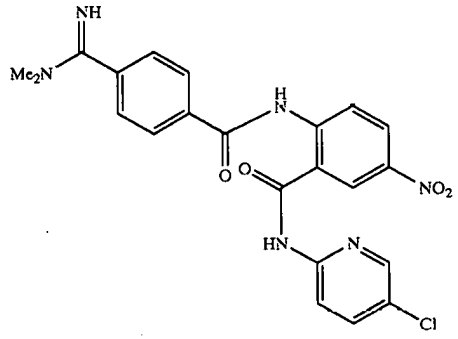
MS (M+H):430

Example 287



MS (M+H):446

Example 288

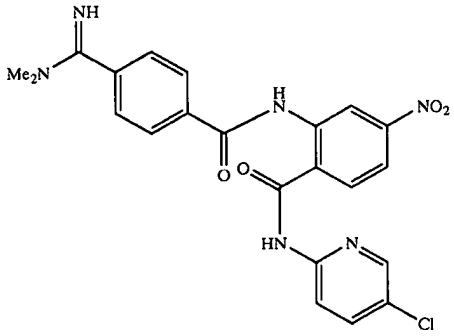


Step 1: A solution of methyl 2-amino-5-nitrobenzoate (1 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 1 h. The resulting mixture was quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give the desired product.

Step 2: A solution of 2-amino-5-bromopridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added the compound obtained in step 1 (0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and purified by column chromatography to give the desired product.

Step 3: The product obtained in step 2 was subjected to standard Pinner conditions to give the title compound after HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN). MS $(M+H)^+$: 467.

Example 289

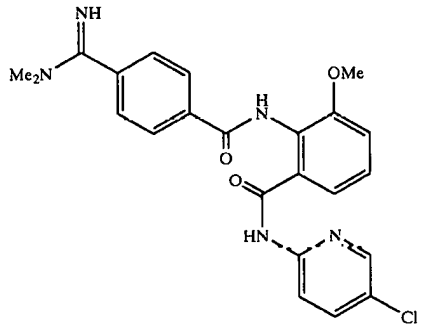


This compound was prepared according to the procedure previously described. MS $(M+H)^+$: 467.

Example 290–302

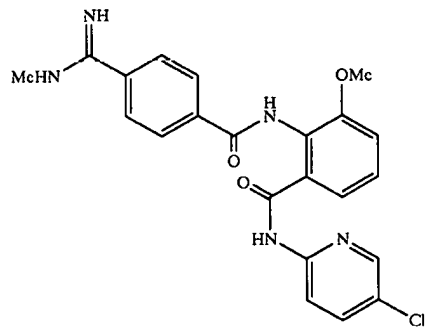
The following compounds were prepared according to the procedure previously described.

Example 297



MS (M+H):452

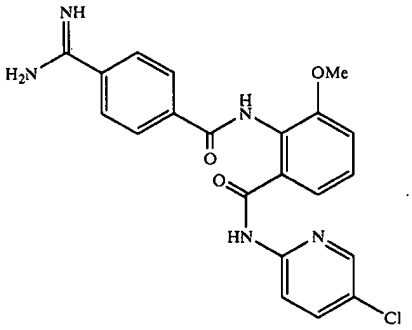
Example 298



MS (M+H):438

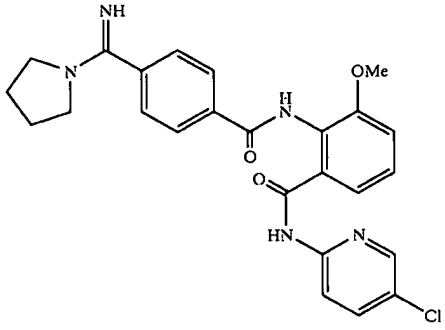
-continued

Example 299



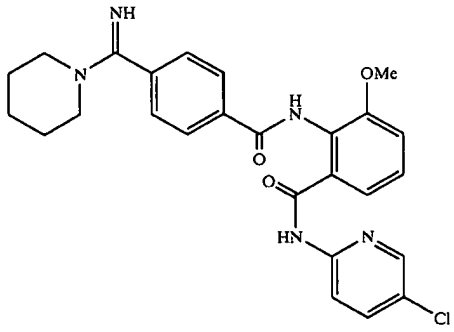
MS (M+H):424

Example 300



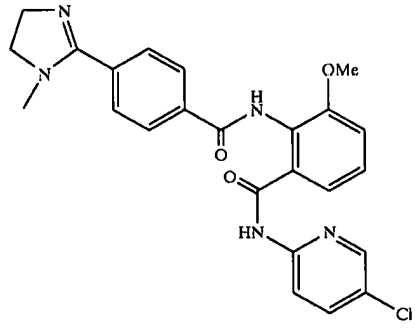
MS (M+H):478

Example 301



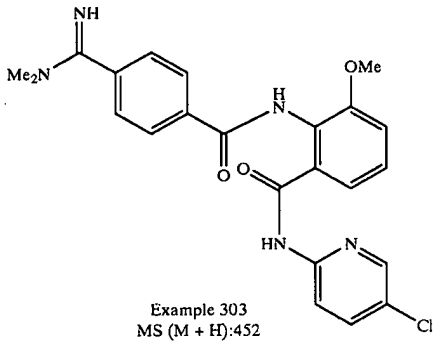
MS (M+H):492

Example 302



MS (M+H):484

Example 303

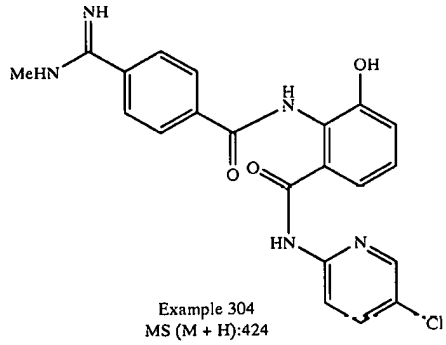


Example 303
MS (M + H):452

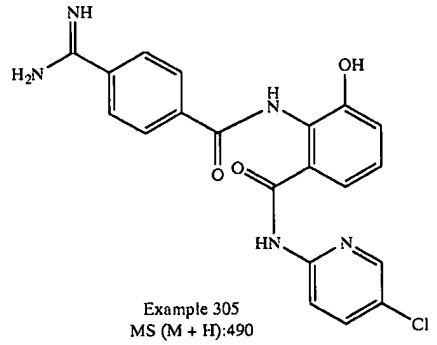
Example 297 (1 equiv) in CH_2Cl_2 was treated with BBr_3 (4 equiv) overnight, quenched with ice water. HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN) gave the title compound. MS $(M+H)^+$: 438.

Example 304–308

The following compounds were prepared according to the procedure previously described.

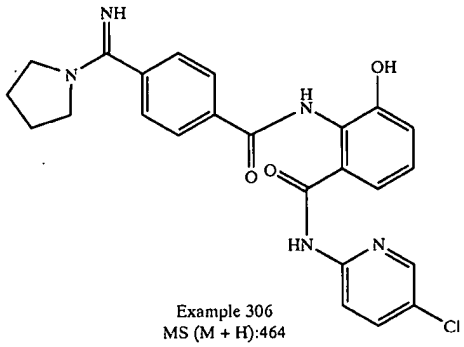


Example 304
MS (M + H):424

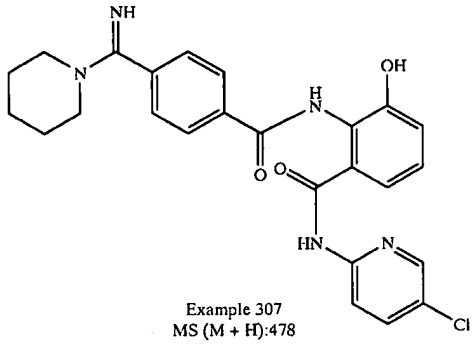


Example 305
MS (M + H):490

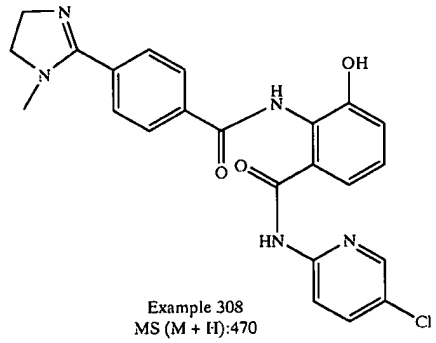
-continued



Example 306
MS (M + H):464



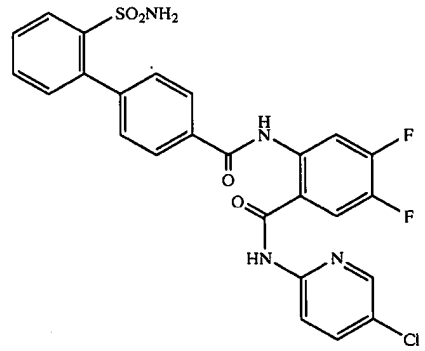
Example 307
MS (M + H):478



Example 308
MS (M + H):470

Example 309

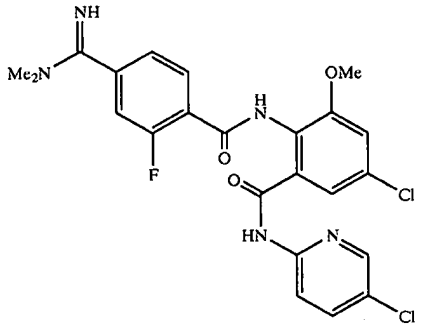
This compound was prepared according to the procedure previously described. MS $(M+H)^+$: 543.



Example 310–315

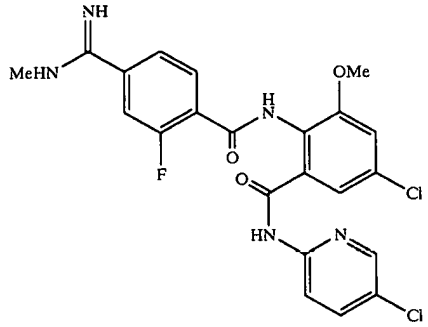
The following compounds were prepared according to the procedure previously described.

Example 310



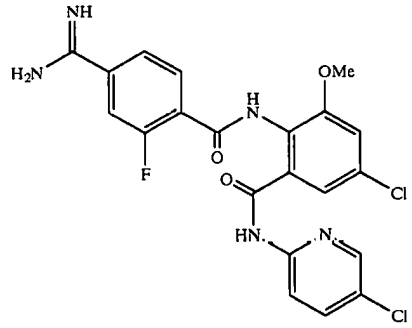
MS (M+H):504

Example 311



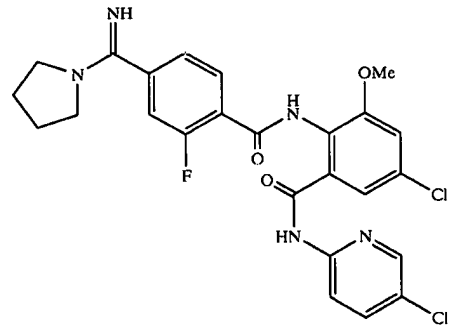
MS (M+H):490

Example 312



MS (M+H):476

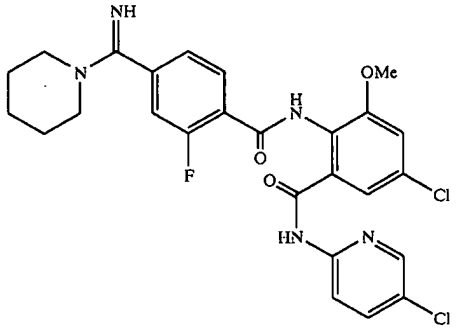
Example 313



MS (M+H):530

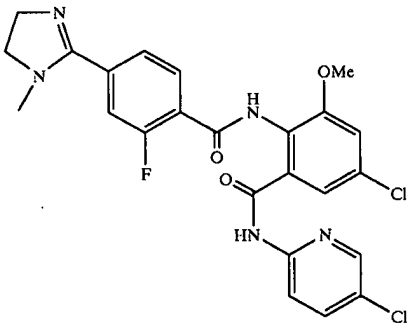
-continued

Example 314



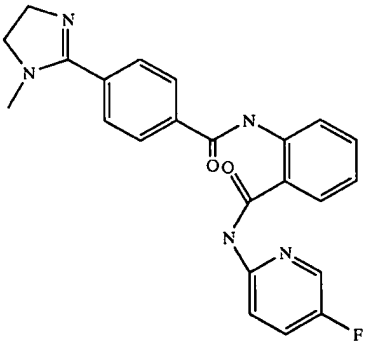
MS (M+H):544

Example 315



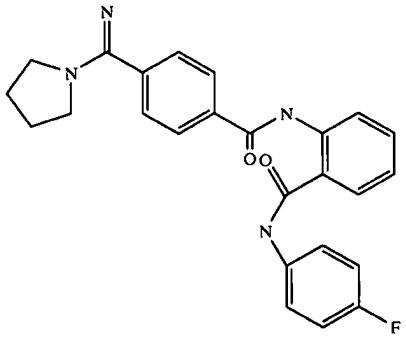
MS (M+H):516

Example 316



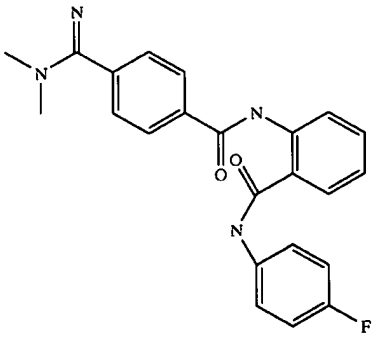
The title compound was synthesized according to the procedure described previously. ES-MS 417(M+1).

Example 317



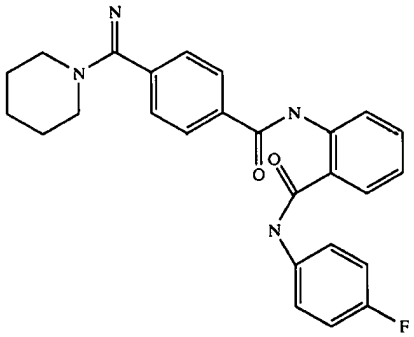
The title compound was synthesized according to the procedure described previously. ES-MS 431(M+1).

Example 318



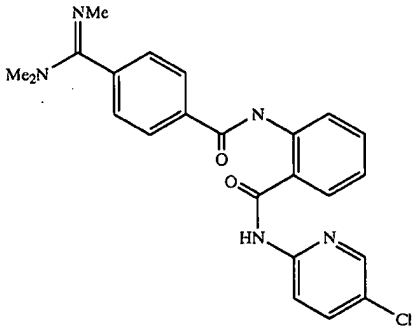
The title compound was synthesized according to the procedure described previously. ES-MS 404(M+1).

Example 319



The title compound was synthesized according to the procedure described previously. ES-MS 445(M+1).

Example 320

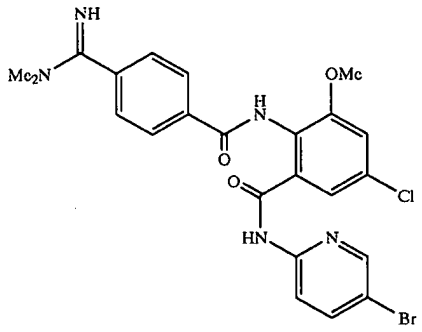


Example 53 (15 mg) was refluxed in pyridine in the presence of 0.1 mL of MeI overnight. The volatile was evaporated and the residue was purified by HPLC to give example 403. MS (M+H): 436.

Examples 321–322

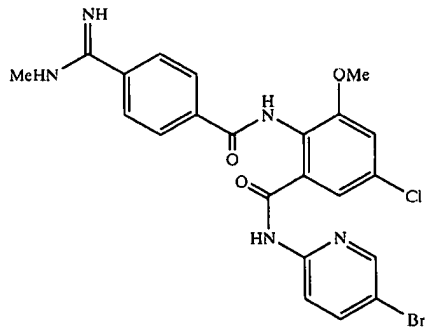
The following compounds were prepared according to the procedure previously described.

Example 321



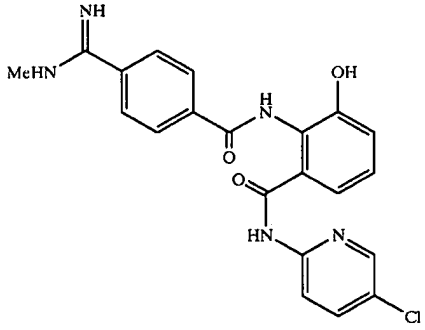
MS (M+H):530

Example 322



MS (M+H):516

Example 323

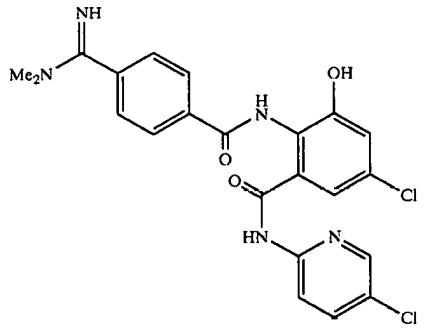


Compound 304 (20 mg) was dissolved in 10 mL of CH_2Cl_2 and was treated with 2 mL of BBr_3 (1N in CH_2Cl_2) overnight. The reaction was quenched with water and reverse phase HPLC gave the desired product. ES-MS 424 (M+H).

Example 324–336

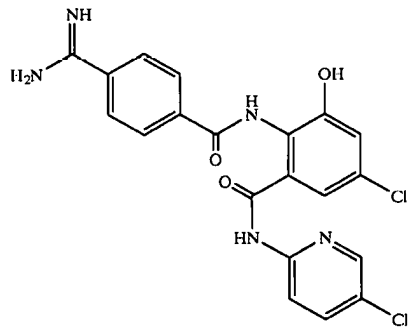
The following compounds were prepared according to the procedure previously described.

Example 324



MS (M+H):472

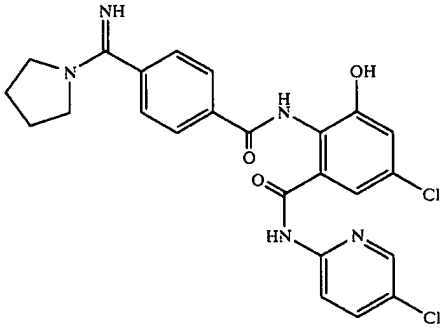
Example 325



MS (M+H):444

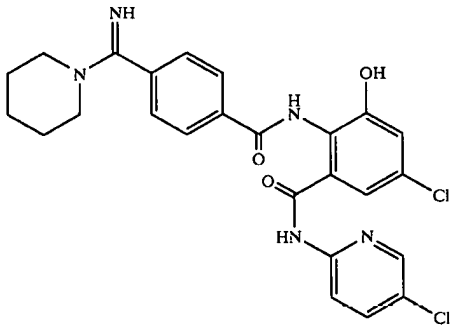
-continued

Example 326



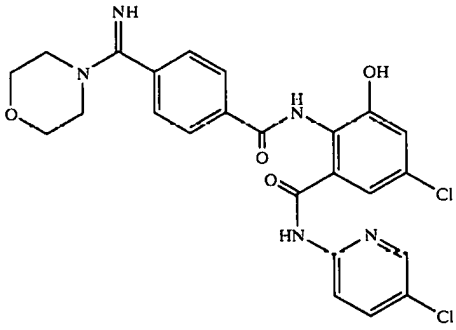
MS (M+H):498

Example 327



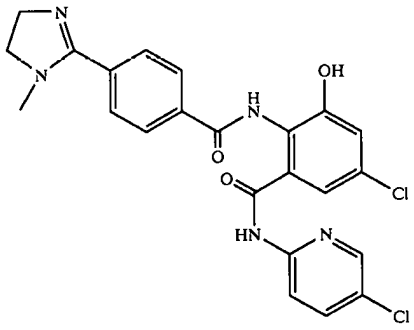
MS (M+H):512

Example 328



MS (M+H):514

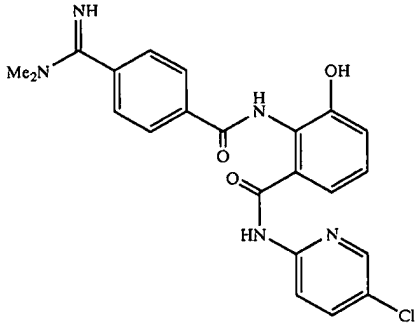
Example 329



MS (M+H):484

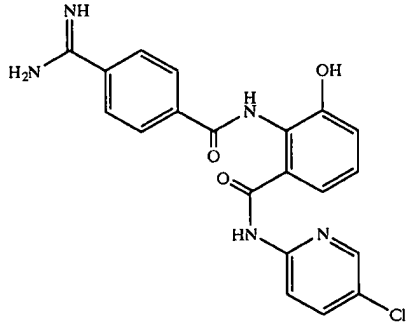
-continued

Example 330



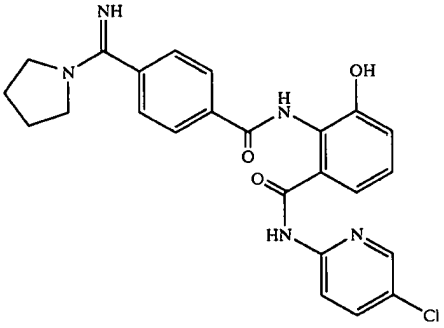
MS (M+H):438

Example 331



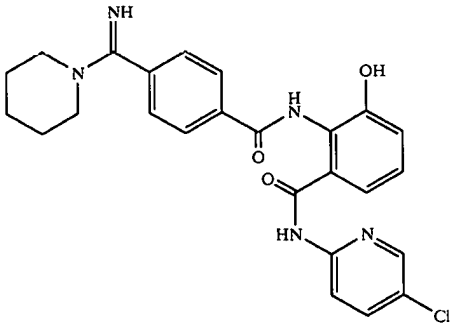
MS (M+H):410

Example 332



MS (M+H):464

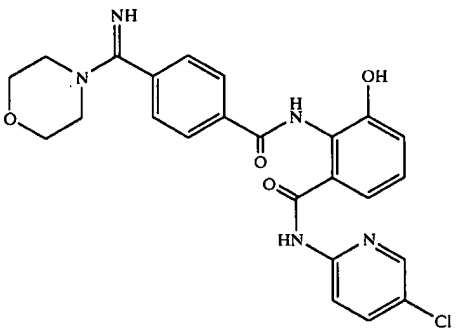
Example 333



MS (M+H):478

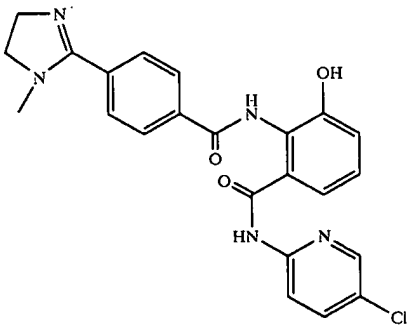
-continued

Example 334



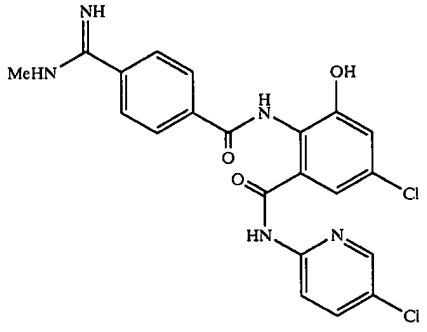
MS (M+H):480

Example 335



MS (M+H):450

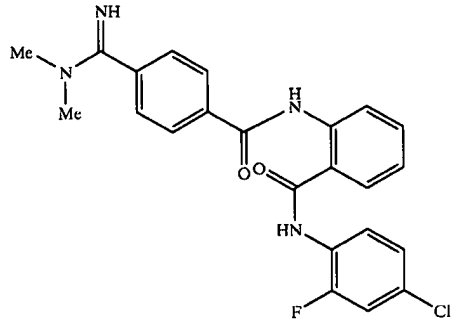
Example 336



MS (M+H):458

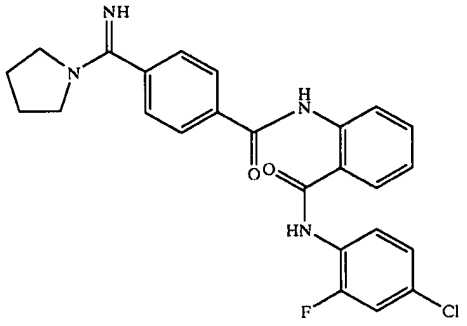
Example 337–344

The following compounds were prepared according to the procedure previously described.

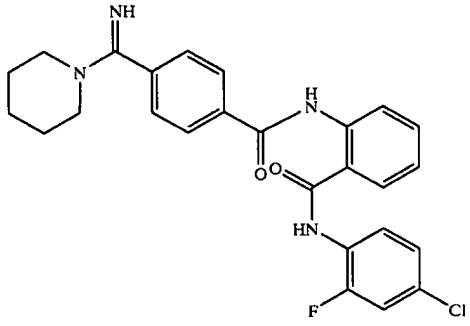


Eample 337
MS (M + H): 439

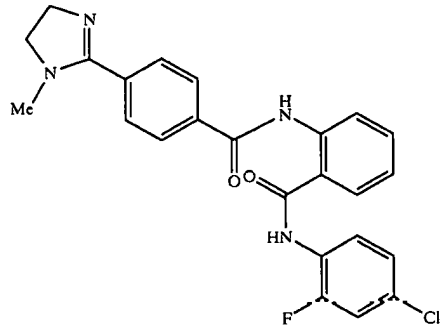
-continued



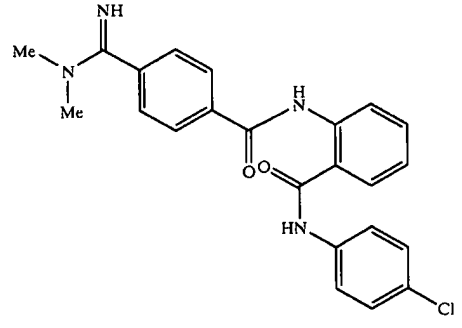
Eample 338
MS (M + H): 465



Eample 339
MS (M + H): 479

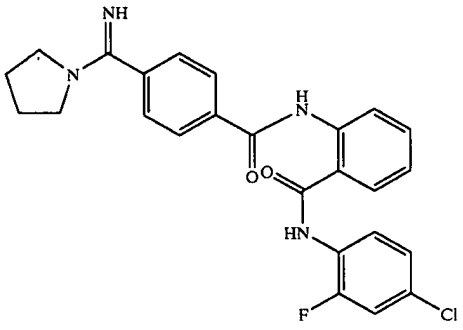


Eample 340
MS (M + H): 451

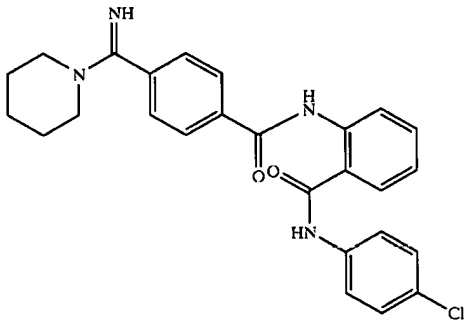


Eample 341
MS (M + H): 421

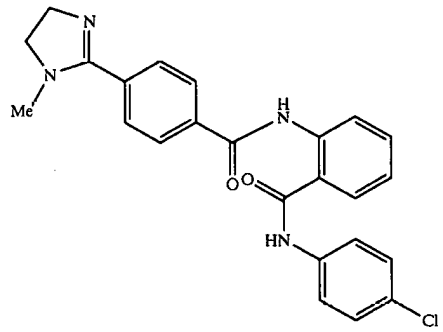
-continued



Eample 342
MS (M + H): 447



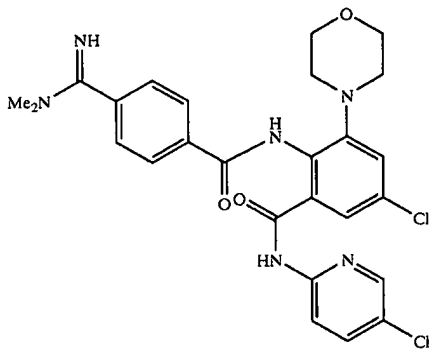
Eample 343
MS (M + H): 461



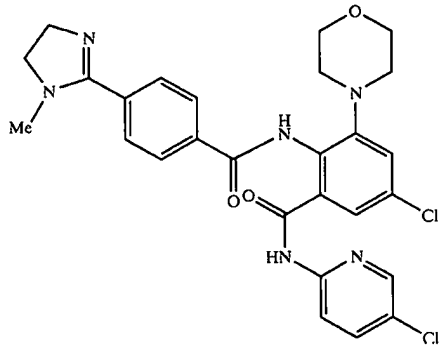
Eample 344
MS (M + H): 433

Example 345–360

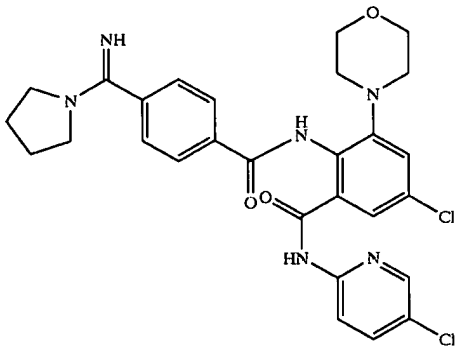
The following compounds were prepared according to the procedure previously described.



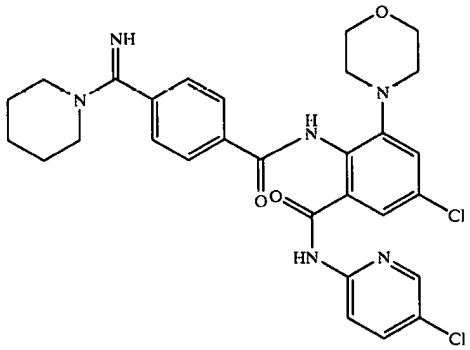
Eample 345
MS (M + H): 541



Eample 346
MS (M + H): 553

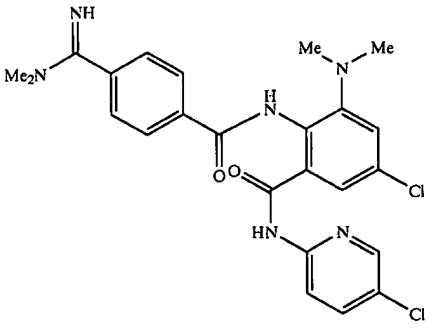


Eample 347
MS (M + H): 567

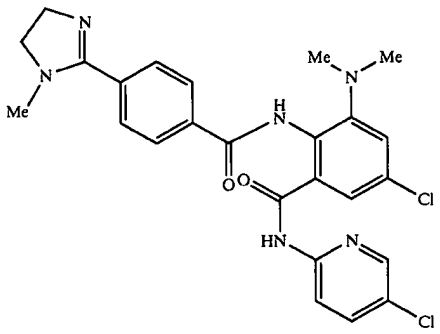


Eample 348
MS (M + H): 581

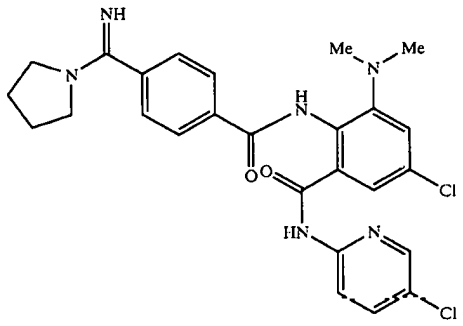
-continued



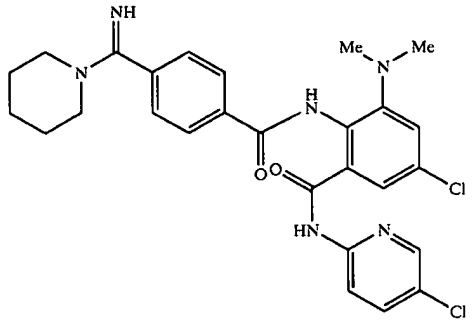
Eample 349
MS (M + H): 499



Eample 350
MS (M + H): 511

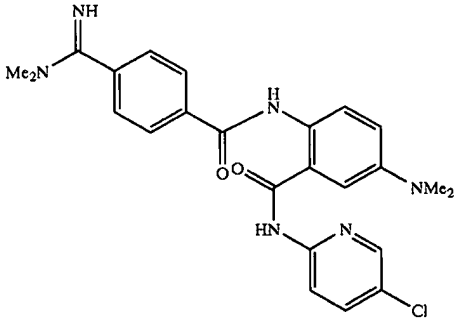


Eample 351
MS (M + H): 525

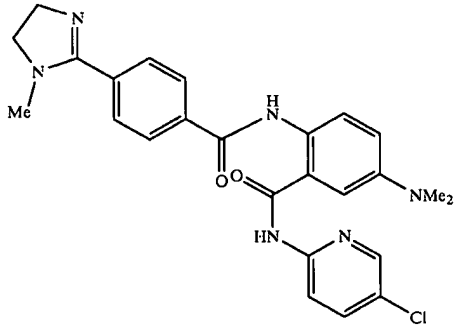


Eample 352
MS (M + H): 539

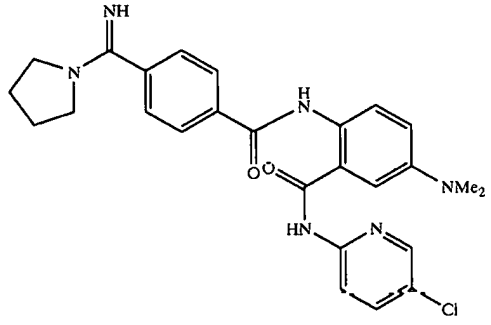
-continued



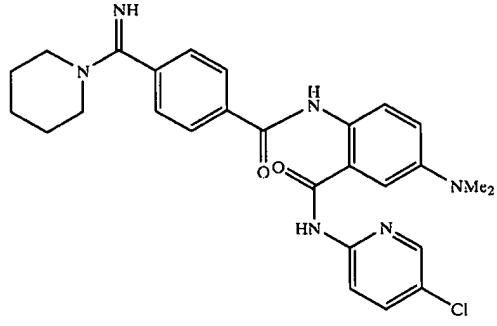
Eample 353
MS (M + H): 499



Eample 354
MS (M + H): 511

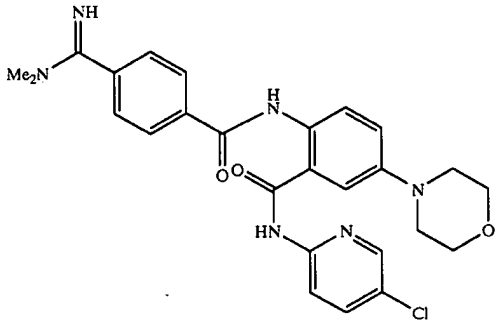


Eample 355
MS (M + H): 525

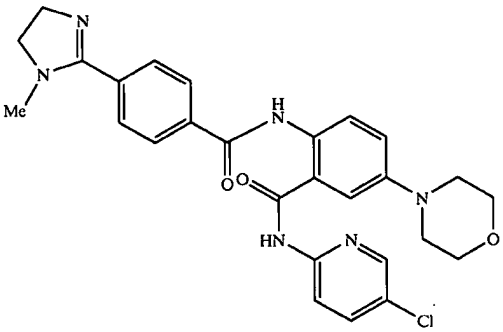


Eample 356
MS (M + H): 539

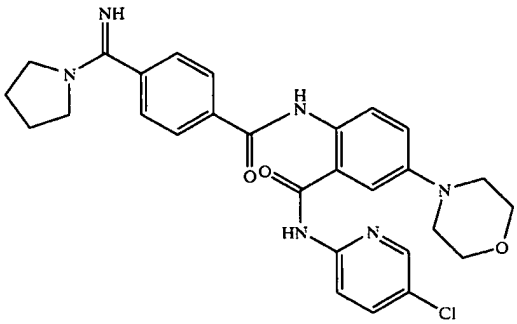
-continued



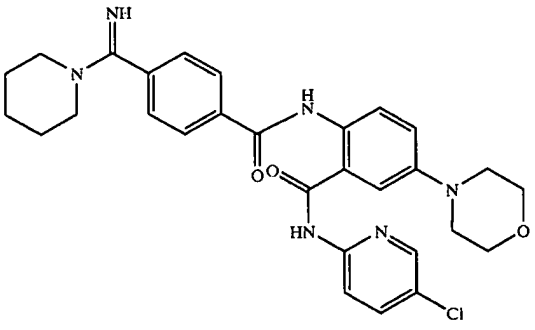
Eample 359
MS (M + H): 541



Eample 358
MS (M + H): 553



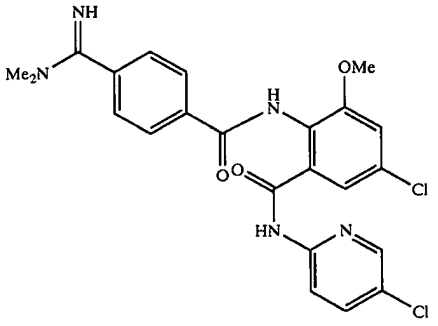
Eample 359
MS (M + H): 567



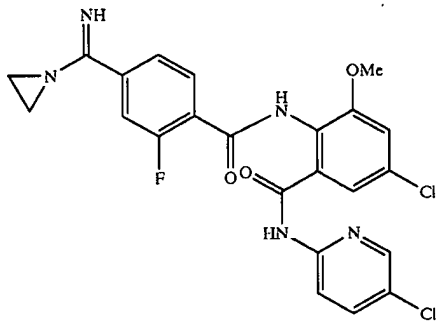
Eample 360
MS (M + H): 581

Example 361–390

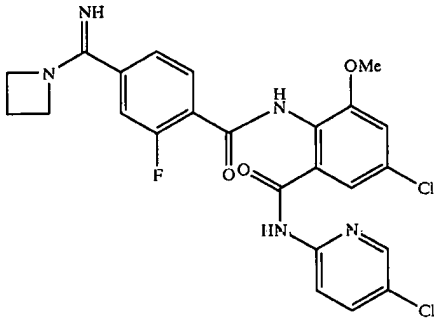
The following compounds were prepared according to the procedure previously described.



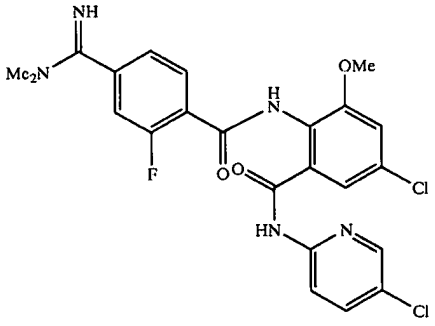
Eample 361
MS (M + H): 500



Eample 362
MS (M + H): 502

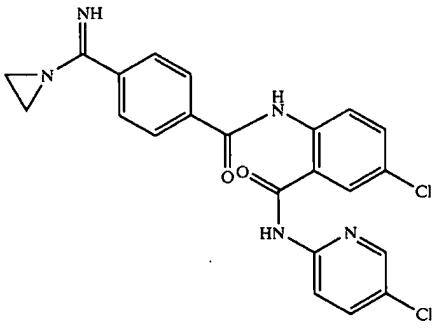


Eample 363
MS (M + H): 514

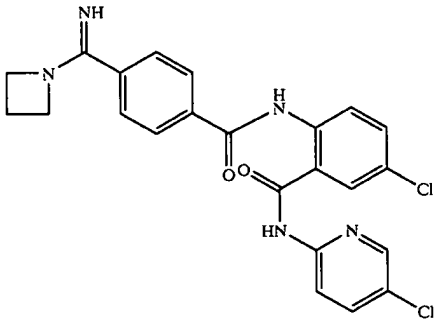


Eample 364
MS (M + H): 512

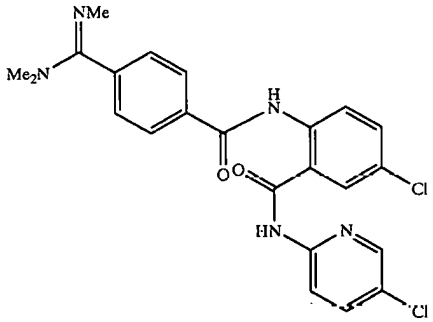
-continued



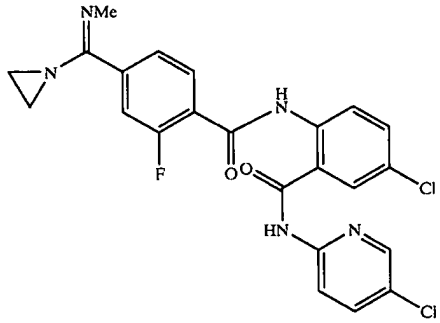
Eample 365
MS (M + H): 454



Eample 366
MS (M + H): 468

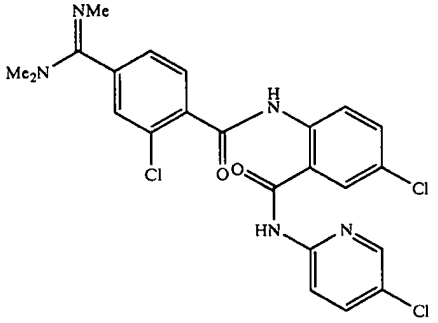


Eample 367
MS (M + H): 466

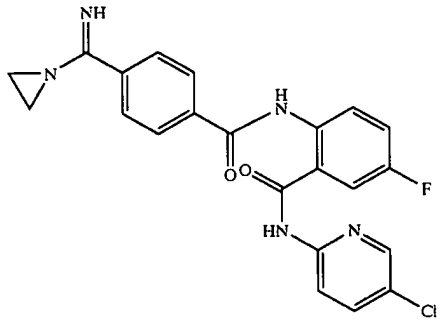


Eample 368
MS (M + H): 472

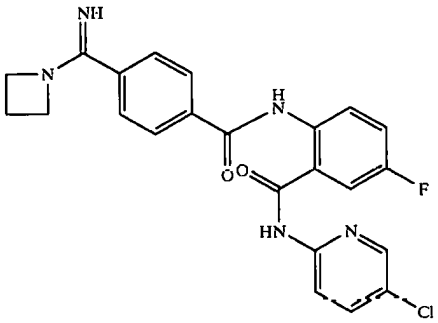
-continued



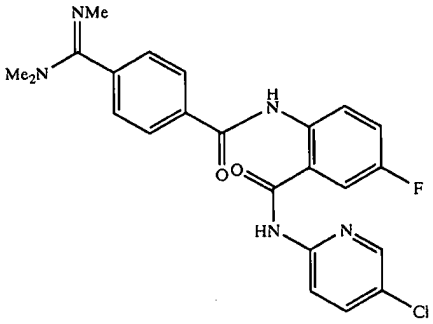
Eample 369
MS (M + H): 504



Eample 370
MS (M + H): 438

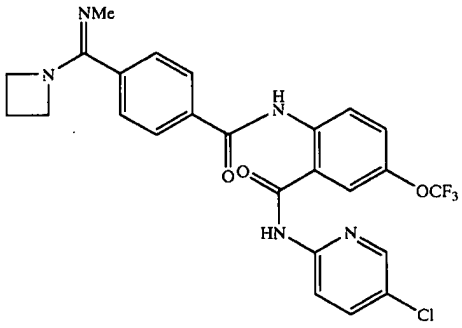


Eample 371
MS (M + H): 452

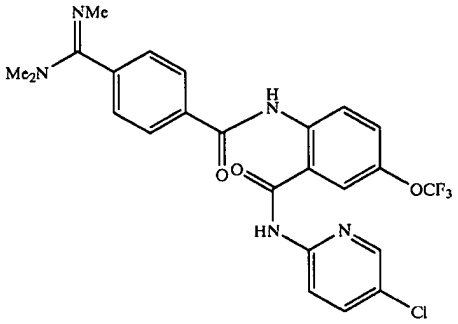


Eample 372
MS (M + H): 450

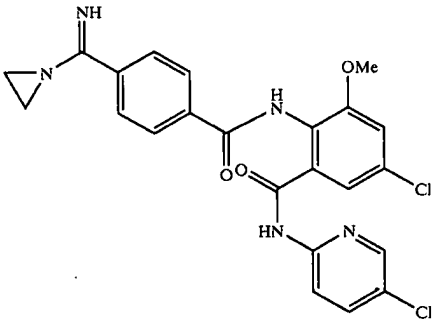
-continued



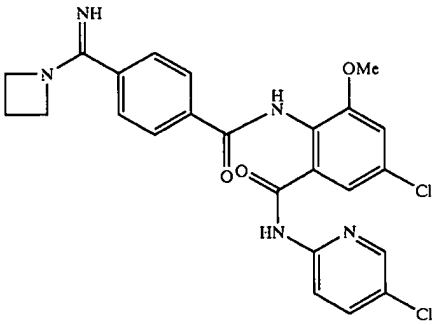
Eample 373
MS (M + H): 515



Eample 374
MS (M + H): 516



Eample 375
MS (M + H): 484



Eample 376
MS (M + H): 498

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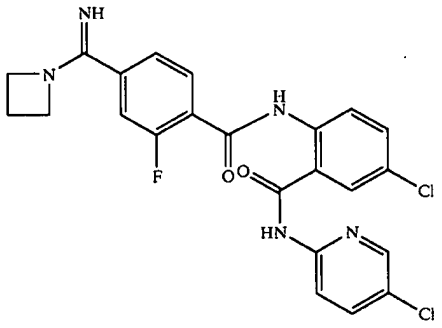
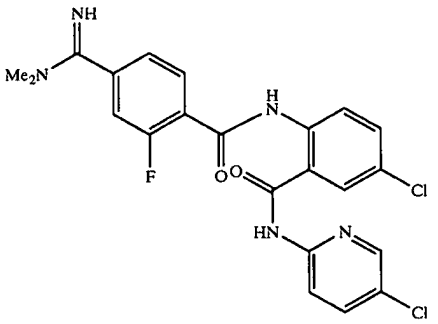
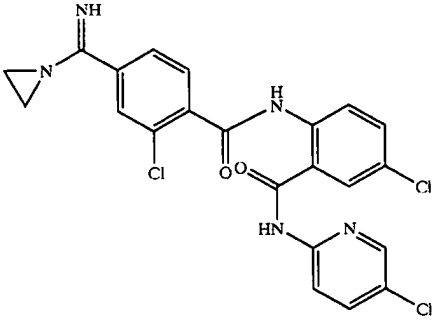


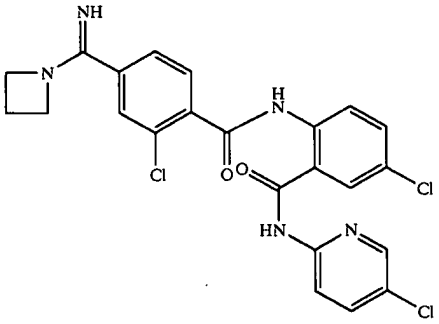
Eample 377
MS (M + H): 486



Eample 378
MS (M + H): 484



Eample 379
MS (M + H): 488



Eample 380
MS (M + H): 502

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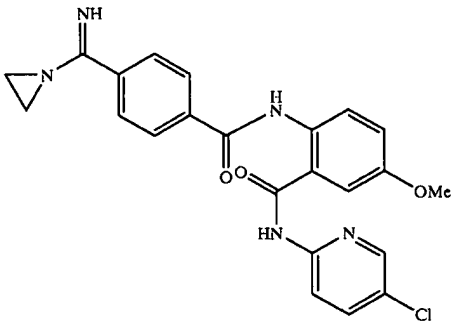
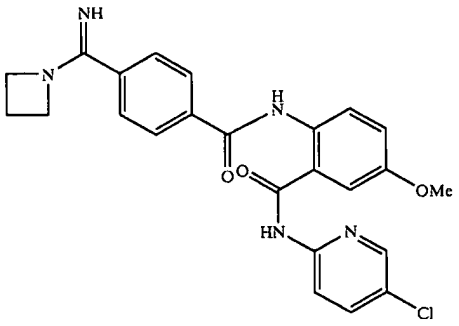
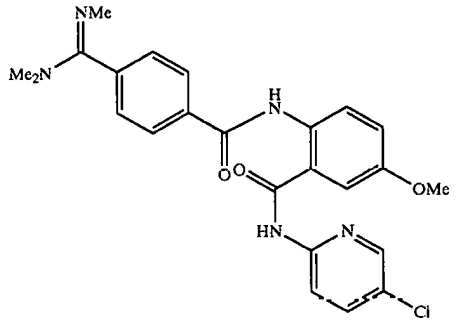


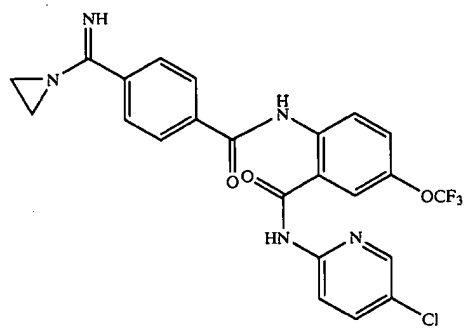
Eample 381
MS (M + H): 450



Eample 382
MS (M + H): 464



Eample 383
MS (M + H): 462



Eample 384
MS (M + H): 504

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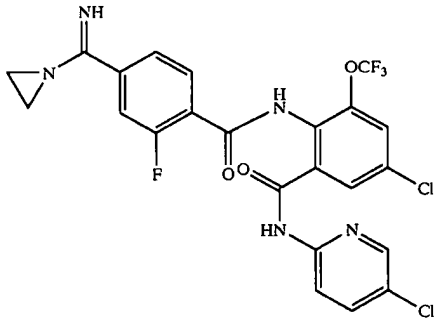
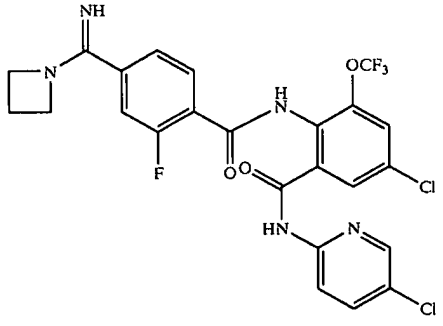
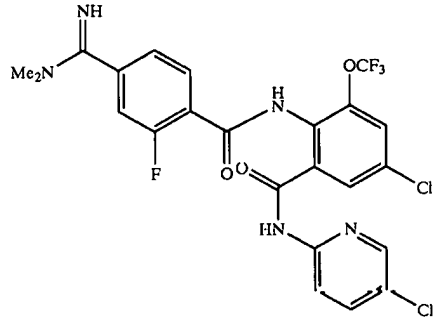


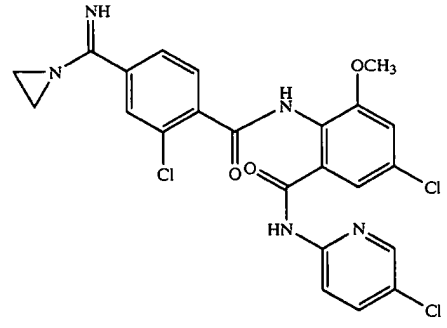
Eample 385
MS (M + H): 556



Eample 386
MS (M + H): 568



Eample 387
MS (M + H): 566



Eample 388
MS (M + H): 518

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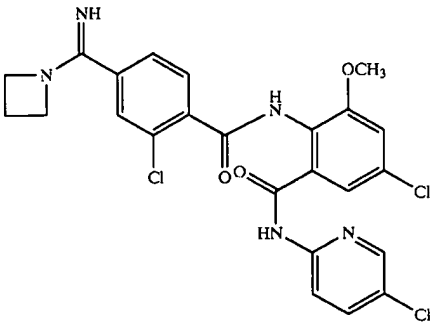
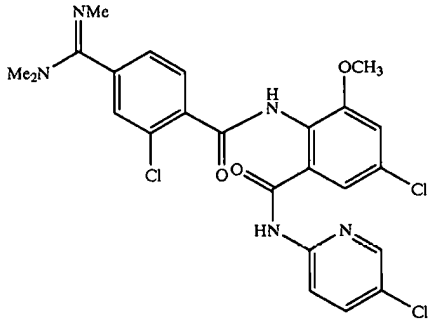


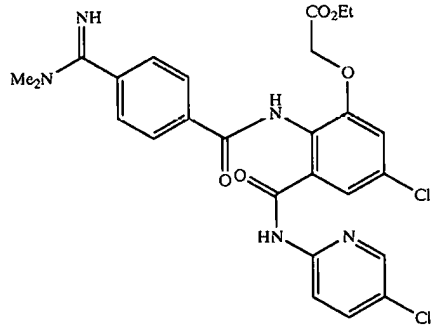
Eample 389
MS (M + H): 532



Eample 390
MS (M + H): 530

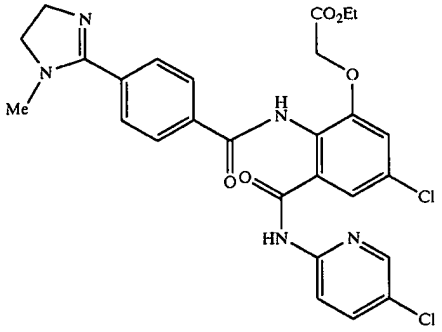
Example 391–398

The following compounds were prepared according to the procedure previously described

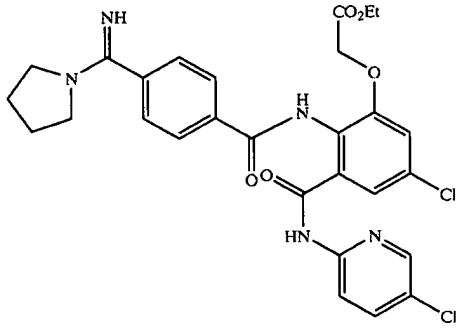


Eample 391
MS (M + H): 558

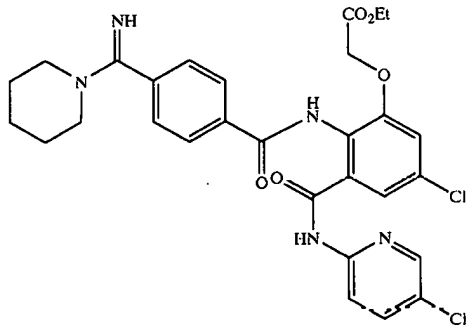
-continued



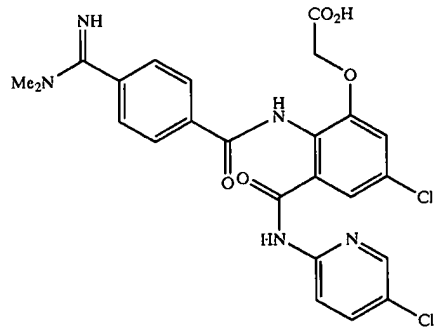
Eample 392
MS (M + H): 570



Eample 393
MS (M + H): 584

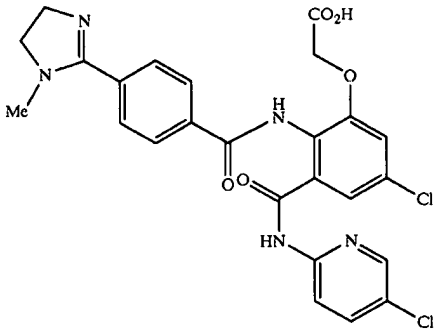


Eample 394
MS (M + H): 598

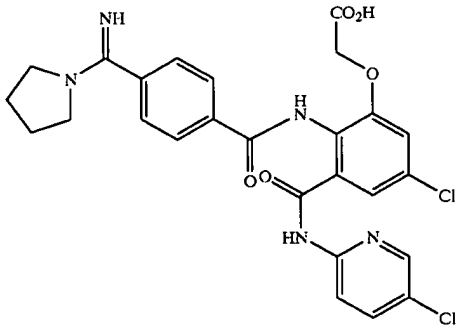


Eample 395
MS (M + H): 530

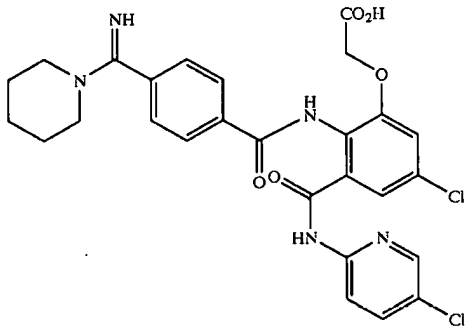
-continued



Eample 396
MS (M + H): 542

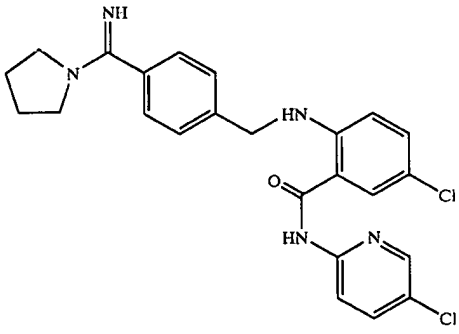


Eample 397
MS (M + H): 556



Eample 398
MS (M + H): 570

Example 399

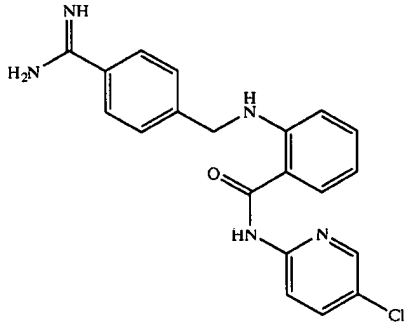


Step 1: A mixture of 4-cyanobenzaldehyde (1 equiv), 4-chloro-2-(5-chloro-2-pyridinyl)amino-carbonyl aniline (1 equiv) and glacial acetic acid (10 equiv) in CH_2Cl_2 was stirred at rt for 30 min. $NaBH(OAc)_3$ (3 equiv) was added at once and the mixture was stirred overnight. The reaction was quenched with water and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product.

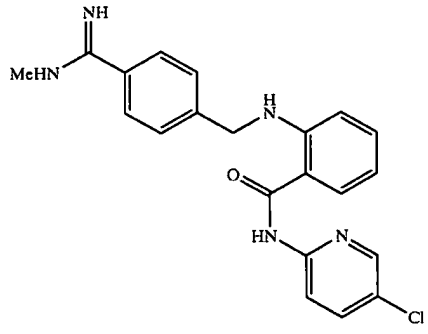
Step 2: A solution of the compound obtained in step 1 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine (0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5 ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M+H) 468.

Examples 400–426

The following compounds were prepared according to the procedure previously described.

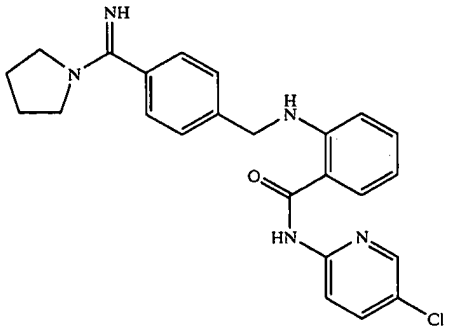


Eample 400
MS (M + H): 414

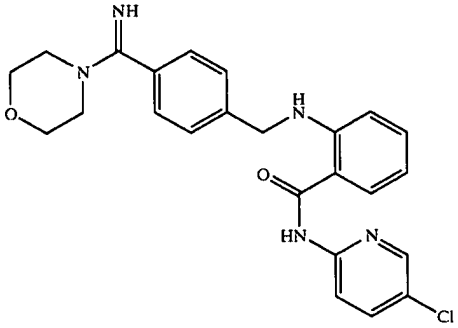


Eample 401
MS (M + H): 428

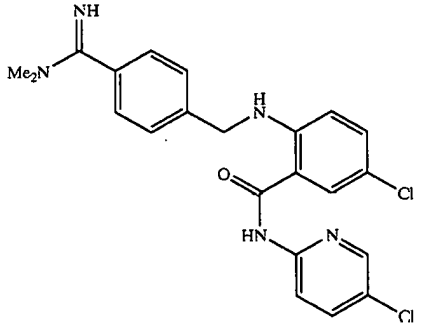
-continued



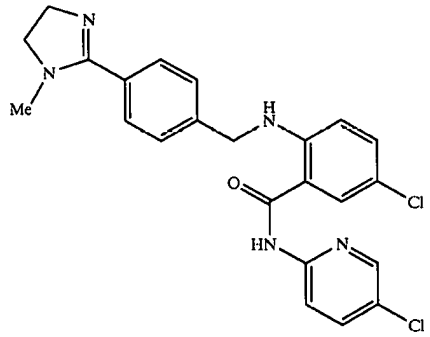
Eample 402
MS (M + H): 468



Eample 403
MS (M + H): 484

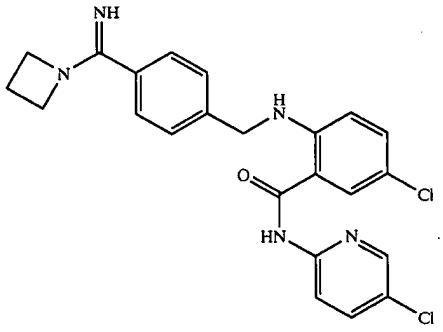


Eample 404
MS (M + H): 442

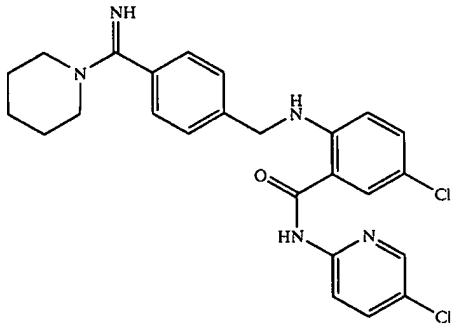


Eample 405
MS (M + H): 428

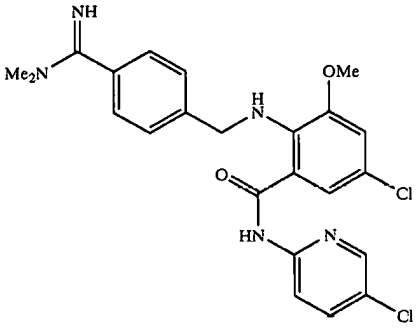
-continued



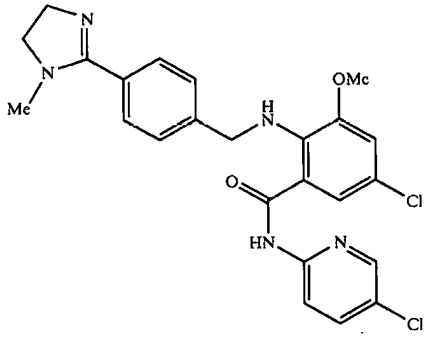
Eample 406
MS (M + H): 468



Eample 407
MS (M + H): 484

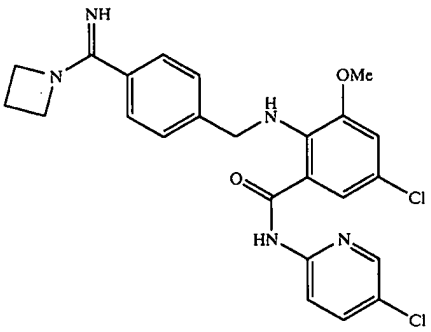


Eample 408
MS (M + H): 472

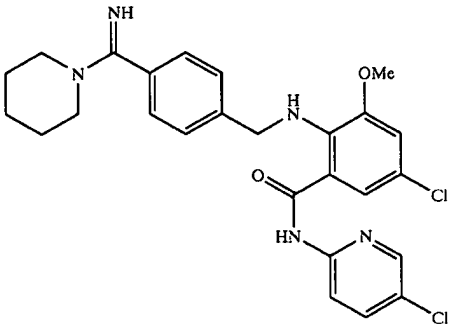


Eample 409
MS (M + H): 484

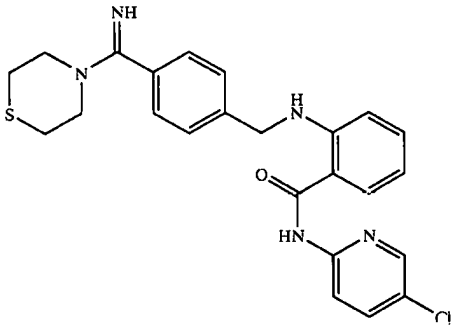
-continued



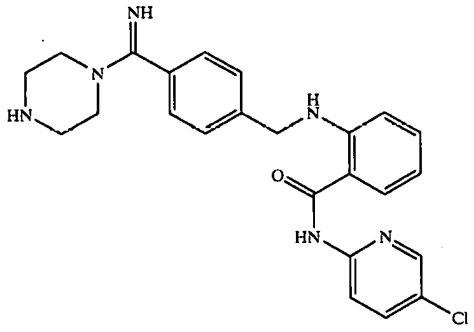
Eample 410
MS (M + H): 484



Eample 411
MS (M + H): 512

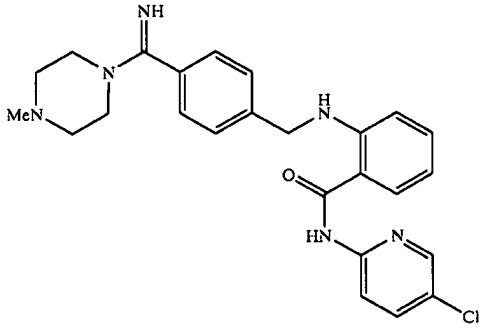


Eample 412
MS (M + H) : 530

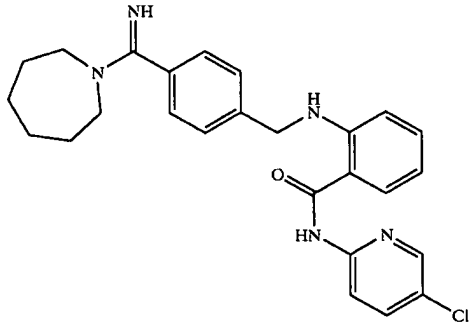


Eample 413
MS (M + H) : 513

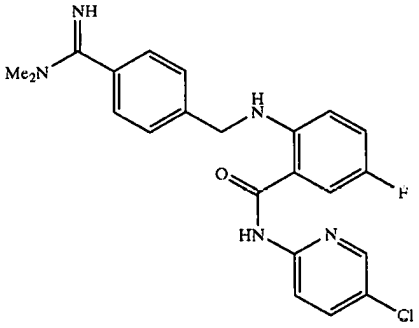
-continued



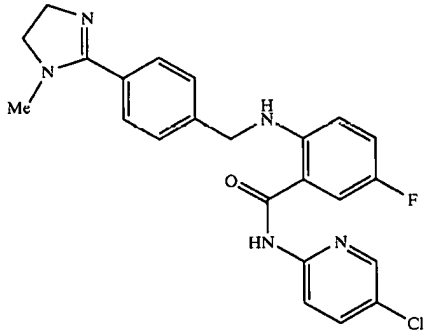
Eample 414
MS (M + H) : 527



Eample 415
MS (M + H) : 526



Eample 416
MS (M + H): 426



Eample 417
MS (M + H): 438

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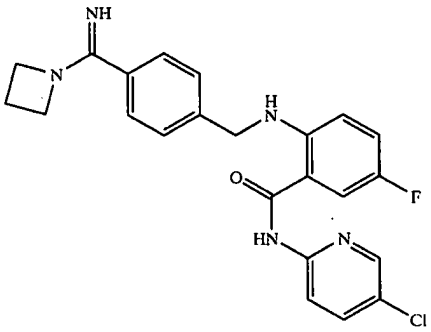
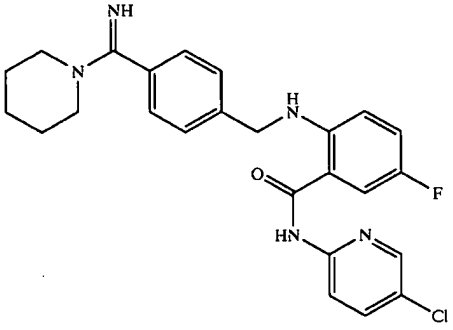
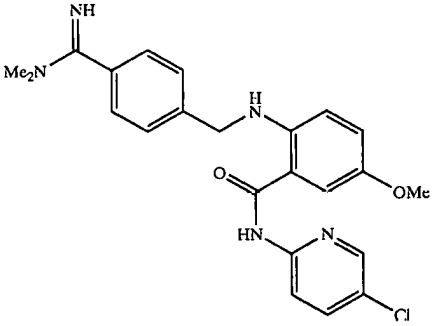


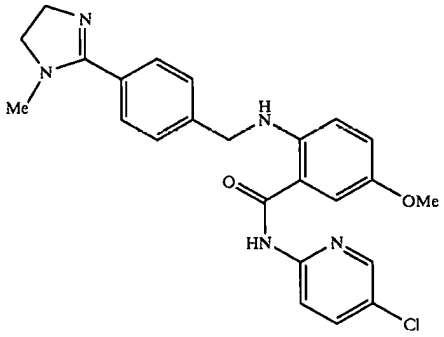
Eample 418
MS (M + H): 438



Eample 419
MS (M + H): 466

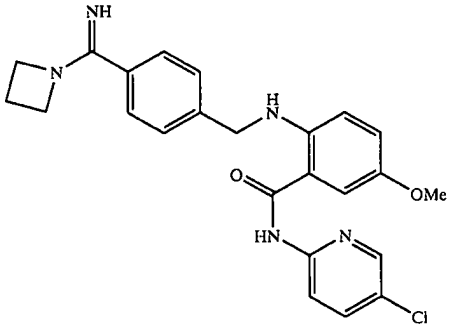


Eample 420
MS (M + H): 438

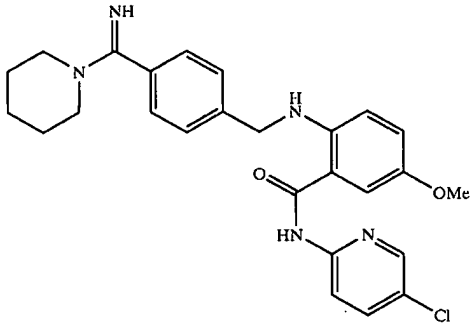


Eample 421
MS (M + H): 450

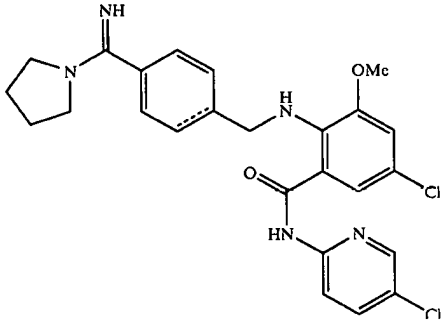
-continued



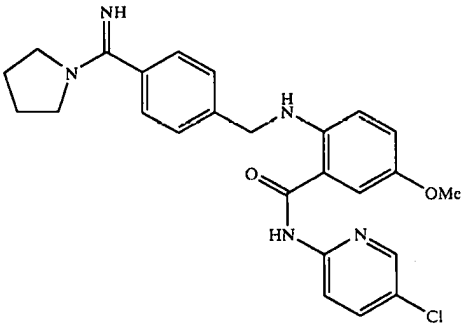
Eample 422
MS (M + H): 450



Eample 423
MS (M + H): 478

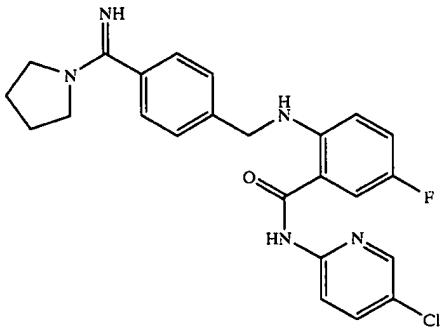


Eample 424
MS (M + H): 498



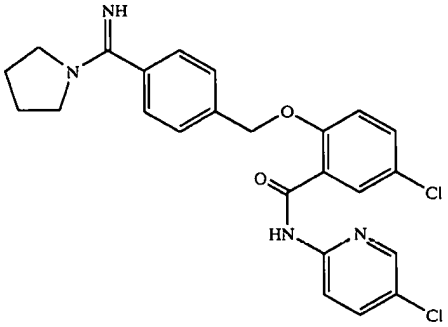
Eample 425
MS (M + H): 464

-continued



Eample 426
MS (M + H): 448

Example 427



Step 1: A mixture of 4-cyanobenzyl bromide (1 equiv), methyl 2-hydroxybenzoate (1 equiv) and cesium carbonate (10 equiv) in DMF was stirred at rt overnight. The mixture was then diluted with EtOAc, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

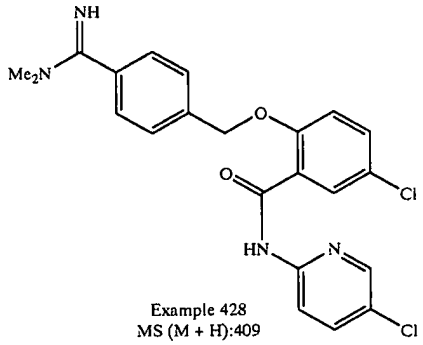
Step 2: A solution of the compound obtained in step 1 (1 equiv) in MeOH was treated with 1N LiOH (2.2 equiv) for 1 h. After removal of methanol and acidifying with 1N HCl to PH ~1, the mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and evaporated to give the product.

Step 3: A solution of the compound obtained in step 2 (1 equiv) in dichloromethane was treated with oxalyl chloride (3 equiv) and 2 drops of DMF at rt for 3 h. The volatile was evaporated and the residue was redissolved in methylenechloride. To the solution was added 2-amino-5-chloropyridine (1 equiv) and pyridine (5 equiv). The mixture was stirred at rt for 2 h, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

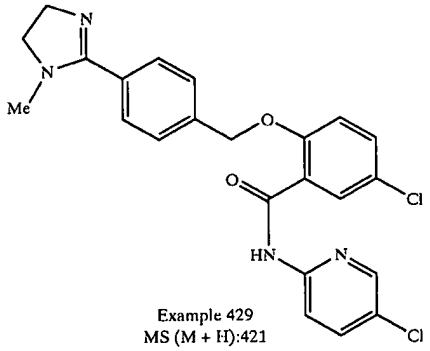
Step 2: A solution of the compound obtained in step 3 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine.(0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5 ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M+H) 435.

Examples 428–431

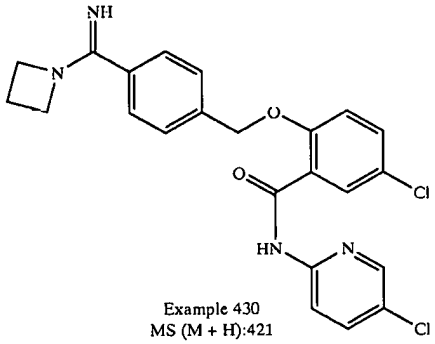
The following compounds were similarly prepared.



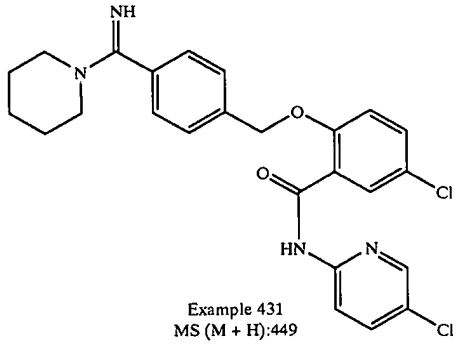
Example 428
MS (M + H):409



Example 429
MS (M + H):421

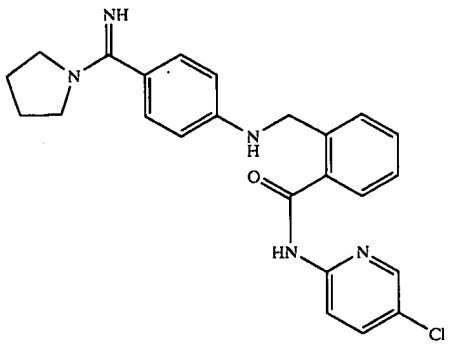


Example 430
MS (M + H):421



Example 431
MS (M + H):449

Example 432



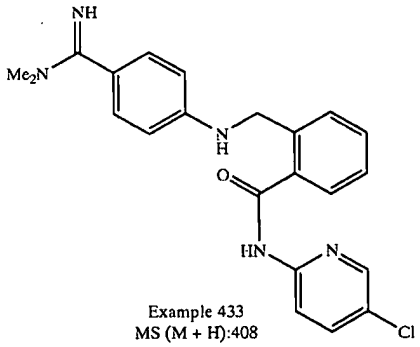
Step 1: A solution of 2-carboxybenzaldehyde (1 equiv) in dichloromethane was treated with oxalyl chloride (3 equiv) and 2 drops of DMF at rt for 3 h. The volatile was evaporated and the residue was redissolved in methylenechloride. To the solution was added 2-amino-5-chloropyridine (1 equiv) and pyridine (5 equiv). The mixture was stirred at rt for 2 h, washed with water, dried over Na_2SO_4, filtered and evaporated to give the product.

Step 2: A mixture of the compound obtained in step 1 (1 equiv), 4-cyanoaniline (1 equiv) and glacial acetic acid (10 equiv) in CH_2Cl_2 was stirred at rt for 30 min. $NaBH(OAc)_3$ (3 equiv) was added at once and the mixture was stirred overnight. The reaction was quenched with water and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product.

Step 3: A solution of the compound obtained in step 2 (15 mg) in anhydrous pyridine (10 mL) and triethyl amine (2 mL) was saturated with hydrogen sulfide gas at 0° C. The mixture was stirred at rt overnight. After concentration, the residue was dissolved in anhydrous acetone (10 mL) and iodomethane (1 mL) was added. The mixture was refluxed for 2 hrs. After concentration, the residue was dissolved in anhydrous methanol (5 mL) and a solution of pyrrolidine (0.5 mL) and acetic acid (0.5 mL) in anhydrous methanol (5 ml) was added. The mixture was refluxed for 15 min. After concentrated, the crude residue was purified by RP-HPLC to give target. MS (M+H) 434.

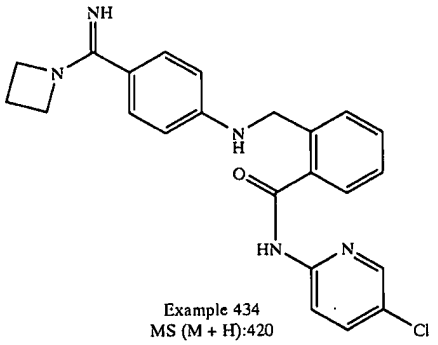
Examples 433–437

The following compounds were similarly prepared.

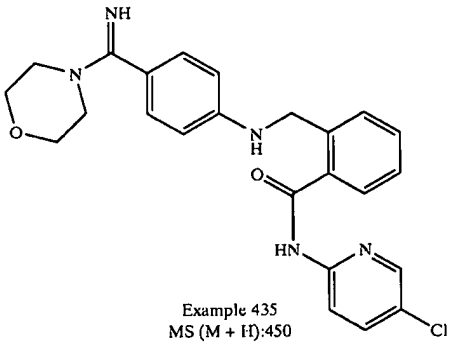


Example 433
MS (M + H):408

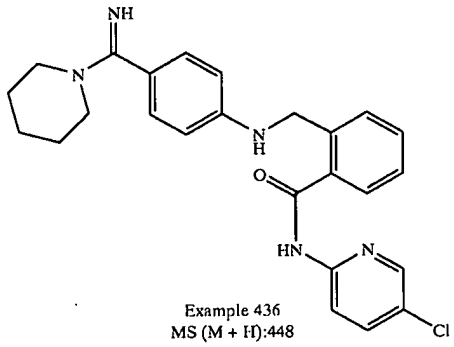
-continued



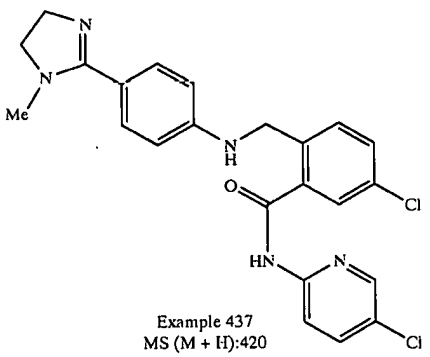
Example 434
MS (M + H):420



Example 435
MS (M + H):450

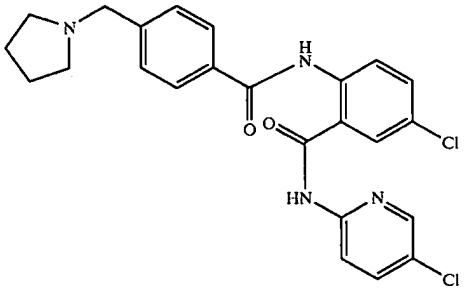


Example 436
MS (M + H):448



Example 437
MS (M + H):420

Example 438

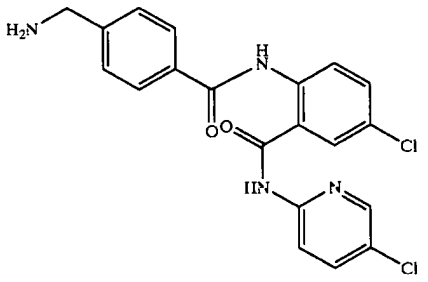


Step 1: A mixture of 4-chloromethylbenzoate chloride (1 equiv), 4-chloro-2-(5-chloro-2-pyridinyl)amino-carbonyl aniline (1 equiv) and pyridine (5 equiv) in CH_2Cl_2 was stirred at reflux for 4 h. The reaction was cooled to rt and the organic layer was washed with brine and dried over Na_2SO_4. Column separation over silica gel gave the desired product (~20% yield).

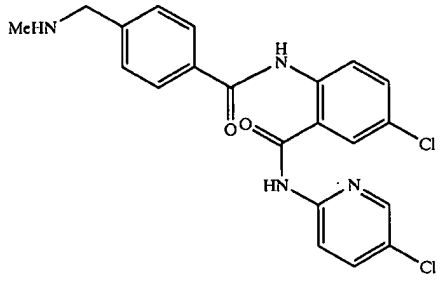
Step 2: A solution of the compound obtained in step 1 (15 mg) in DMF (1 mL) was treated with pyrrolidine (1 mL) at rt overnight. After removing the volatile, the crude residue was purified by RP-HPLC to give the target. MS (M+H) 469.

Example 439–458

The following compounds were prepared according to the procedure previously described.

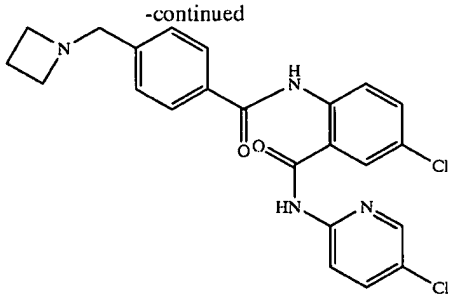


Eample 439
MS (M + H): 415

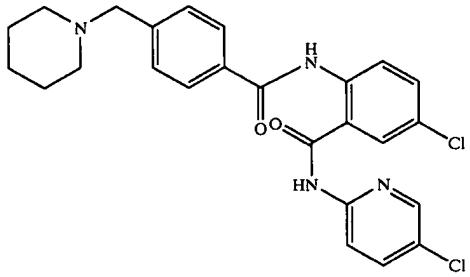


Eample 440
MS (M + H): 429

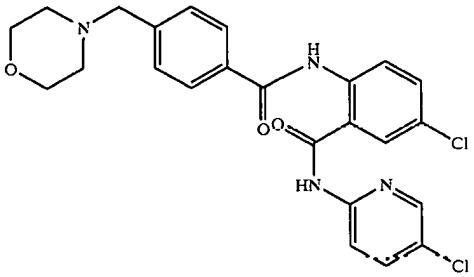
-continued



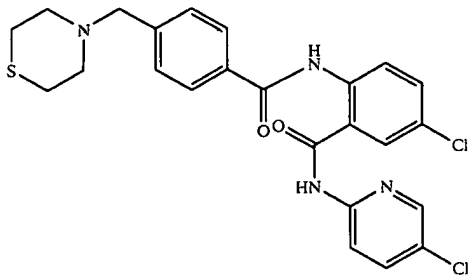
Eample 441
MS (M + H): 455



Eample 442
MS (M + H): 483

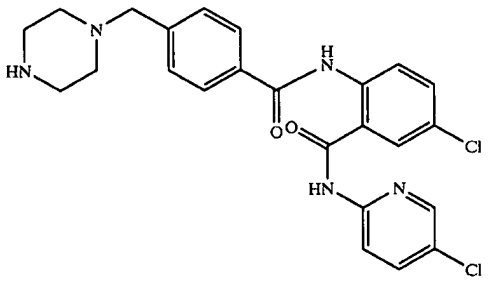


Eample 443
MS (M + H): 485



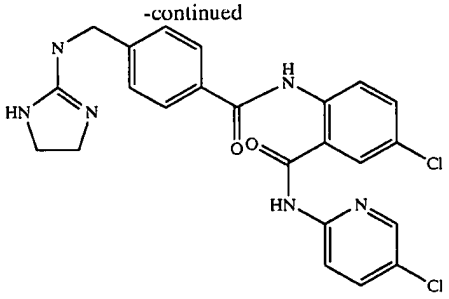
Eample 444
MS (M + H): 501

-continued

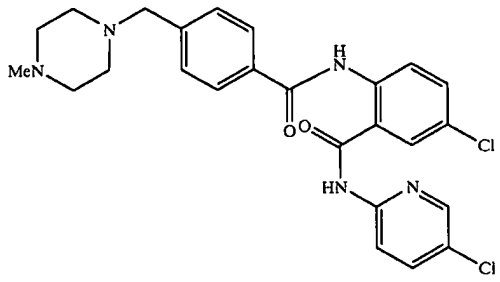


Eample 445
MS (M + H): 484

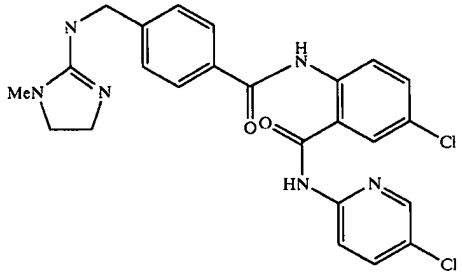
-continued



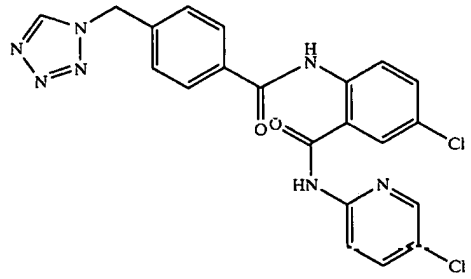
Eample 449
MS (M + H): 483



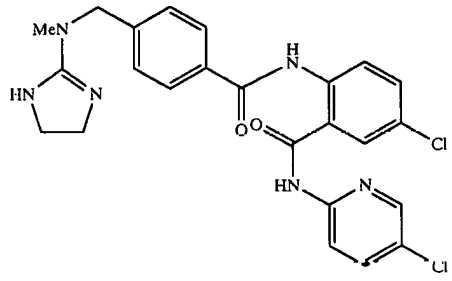
Eample 446
MS (M + H): 498



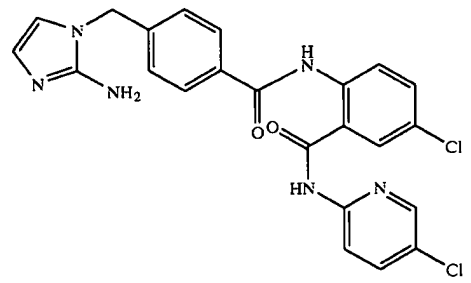
Eample 450
MS (M + H): 497



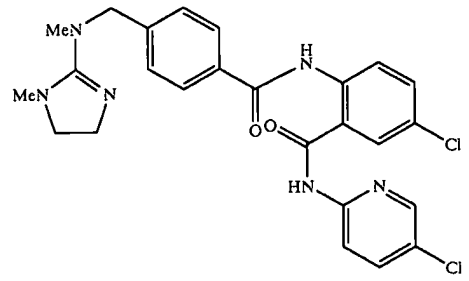
Eample 447
MS (M + H): 468



Eample 451
MS (M + H): 497

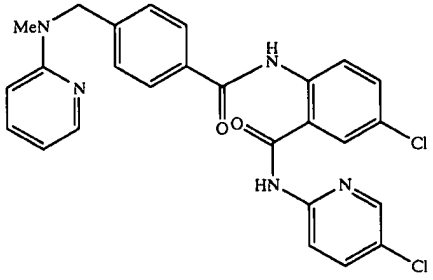


Eample 448
MS (M + H): 481

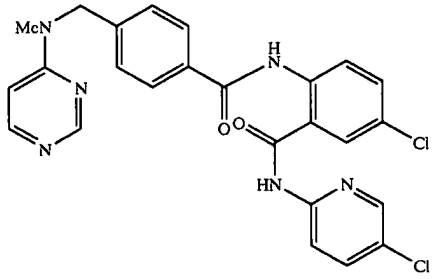


Eample 452
MS (M + H): 511

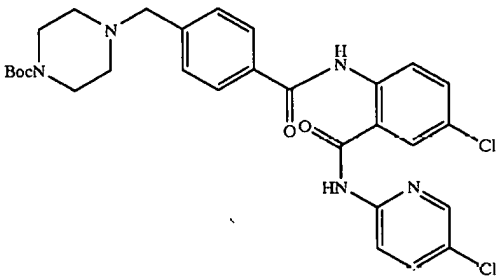
-continued



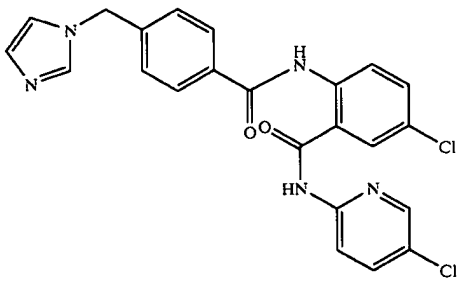
Eample 453
MS (M + H): 506



Eample 454
MS (M + H): 507

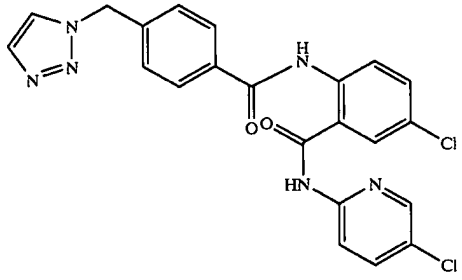


Eample 455
MS (M + H): 539

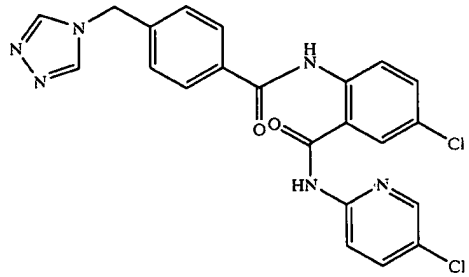


Eample 456
MS (M + H): 466

-continued



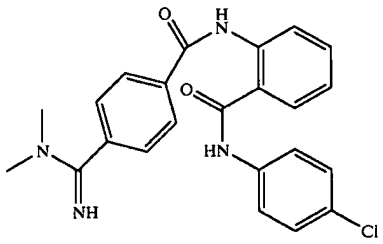
Eample 457
MS (M + H): 467



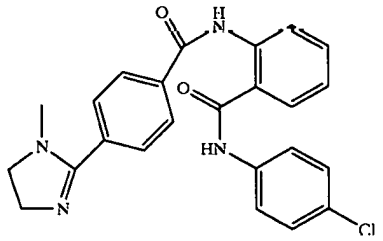
Eample 458
MS (M + H): 467

Example 459–494

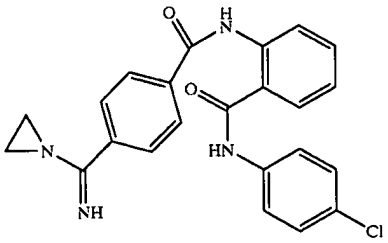
The following compounds were prepared according to the procedure previously described.



MS 421 (M + H)

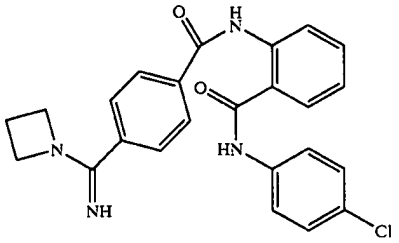


MS 433 (M + H)

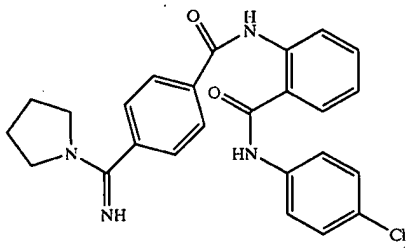


MS 419 (M + H)

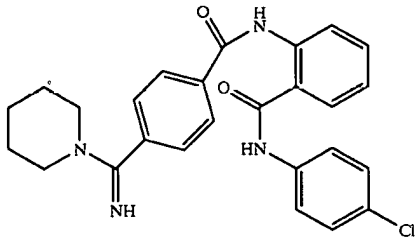
-continued



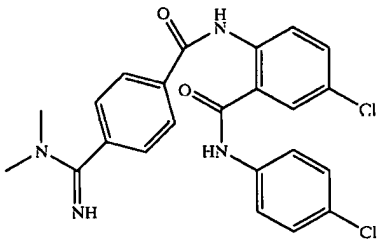
MS 433 (M + H)



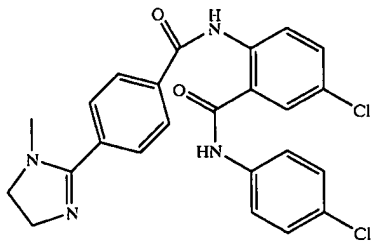
MS 447 (M + H)



MS 461 (M + H)



MS 456 (M + H)



MS 468 (M + H)

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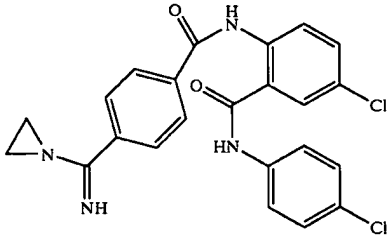
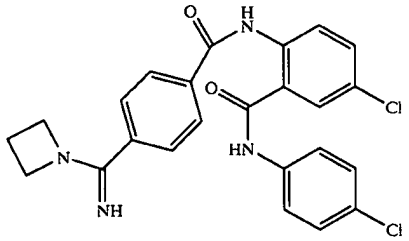
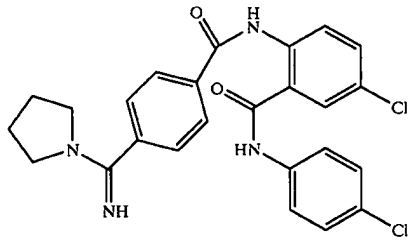


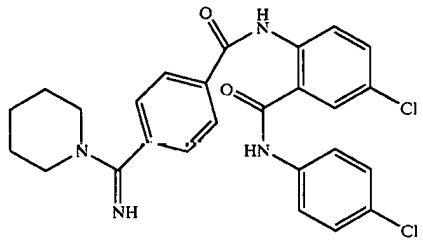
MS 454 (M + H)



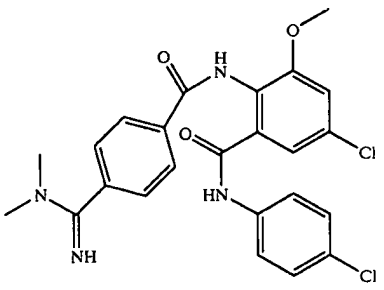
MS 468 (M + H)



MS 482 (M + H)



MS 496 (M + H)



Mol. Wt: 485.36

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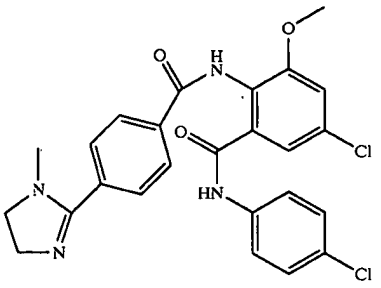
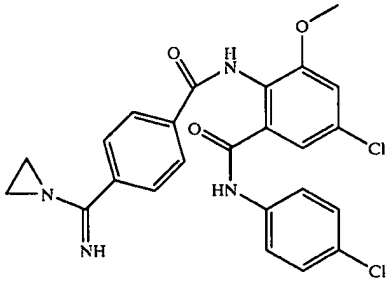
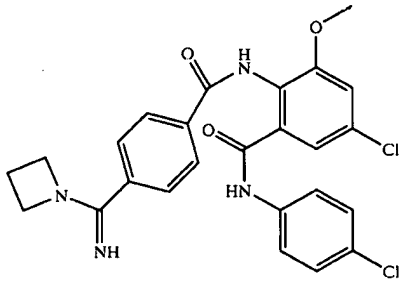


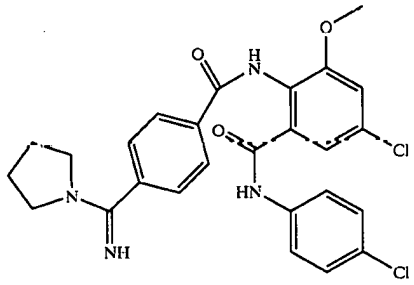
Mol. Wt: 497.37



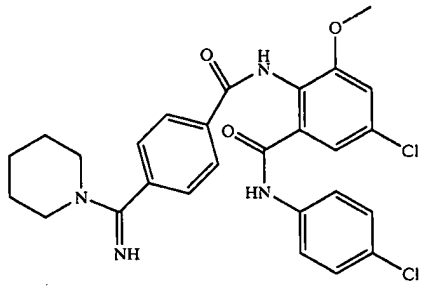
MS 484 (M + H)



MS 498 (M + H)



MS 512 (M + H)



MS 526 (M + H)

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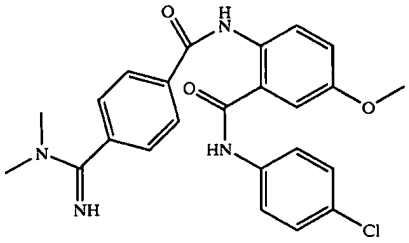
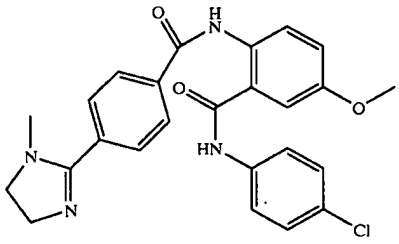
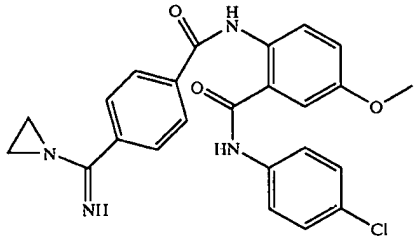


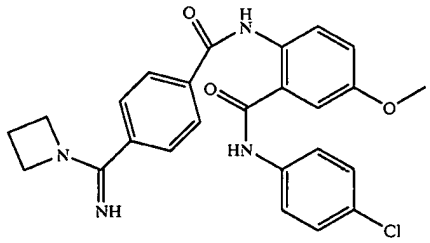
MS 451 (M + H)



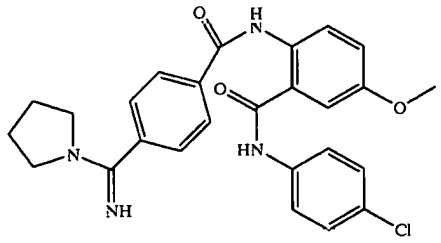
MS 463 (M + H)



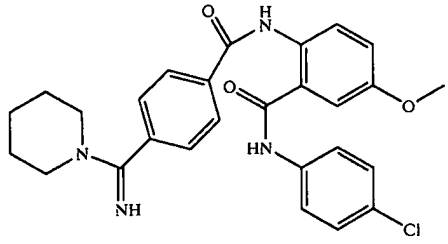
MS 499 (M + H)



MS 463 (M + H)

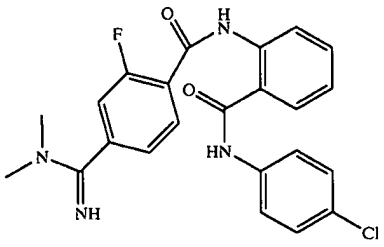


MS 477 (M + H)

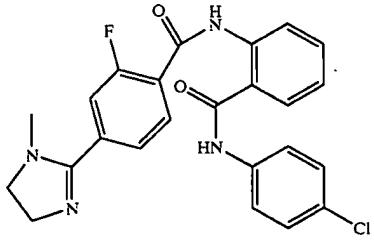


MS 491 (M + H)

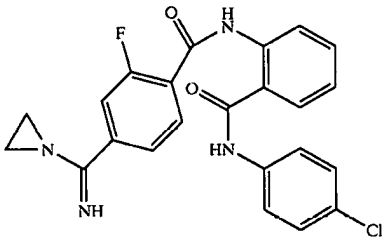
-continued



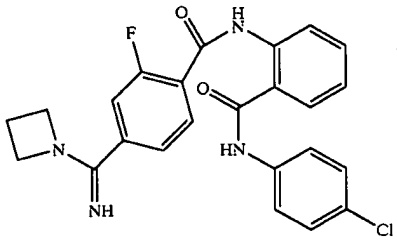
MS 439 (M + H)



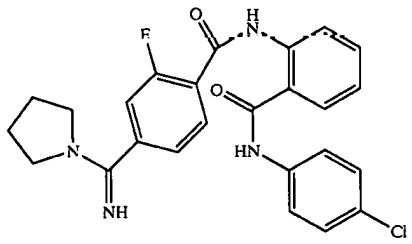
MS 451 (M + H)



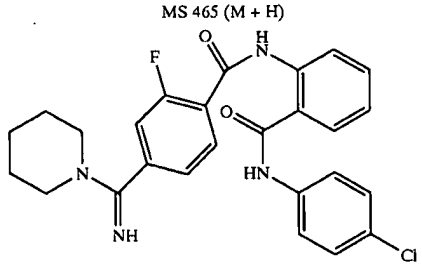
MS 437 (M + H)



MS 451 (M + H)

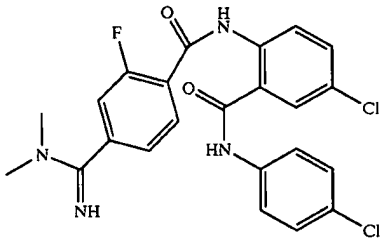


MS 465 (M + H)

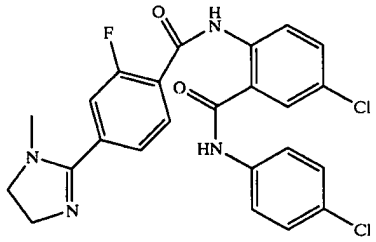


MS 479 (M + H)

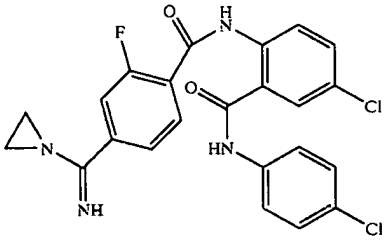
-continued



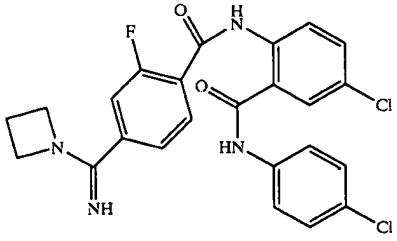
MS 474 (M + H)



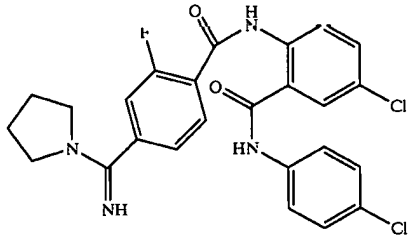
MS 486 (M + 1)



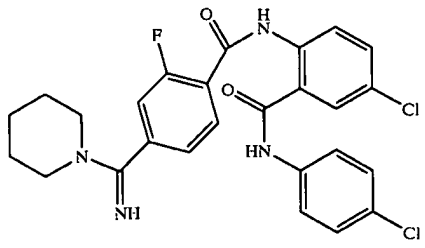
MS 472 (M + H)



MS 484 (M + H)



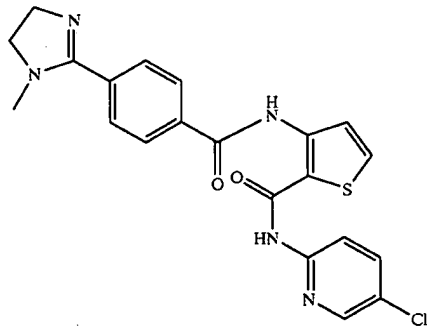
MS 500 (M + H)



MS 514 (M + H)

Example 495

N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide



Preparation of methyl 3-[(4-cyanophenyl)carbonylamino]thiophene-2-carboxylate

A mixture of 4-cyanobenzoyl chloride (1.0500 g, 6.4 mmol), methyl 3-aminothiophenecarboxylate (1.0000 g, 6.4 mmol), and triethylamine (1 mL, 7.0 mmol) in dichloromethane was stirred at room temperature for 18 hours. The mixture was poured into a separatory funnel and washed by 1 N HCl. The organic layers were combined, dried over $MgSO_4$, concentrated in vacuo, and chromatographed through a silica gel column to give the title compound 1.6588 g (91%). ES-MS 287 (M+1):

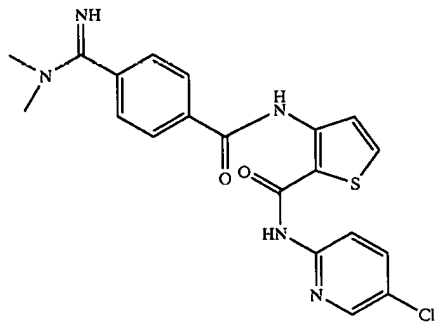
Preparation of N-(2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}(4-cyanophenyl)carboxamide

A portion of 2-amino-5-chloropyridine (68.6 mg, 0.5 mmol) was treated with AlMe3 (0.8 mL, 1.6 mmol), followed by adding the product from step A (160 mg, 0.5 mmol). The mixture was stirred at room temperature for 18 hours. The excess of AlMe3 was killed by 1N HCl solution. The organic layers were combined, dried over $MgSO_4$, concentrated in vacuo, and chromatographed through a silica gel column to give the title compound 0.1528 g (80%). ES-MS 383 (M+1).

A mixture of the product from step B (0.1528 g, 0.4 mmol) and EtOH saturated with HCl was stirred at room temperature for 18 hours. The solvent was removed by a rotovap. The crude oil was treated with 2 mL N-methylethylenediamine for 2 hours until the reaction was complete. Prep HPLC was used to purity the final product. It gave 0.1537 g (88%). ES-MS 440(M+1).

Example 496

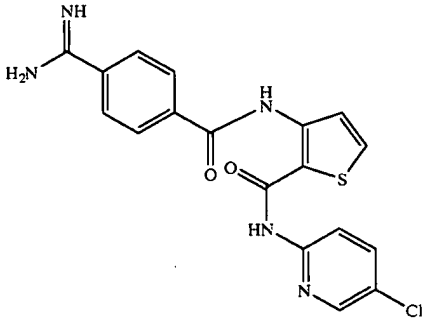
{4-[(dimethylamino)iminomethyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 428 (M+1).

Example 497

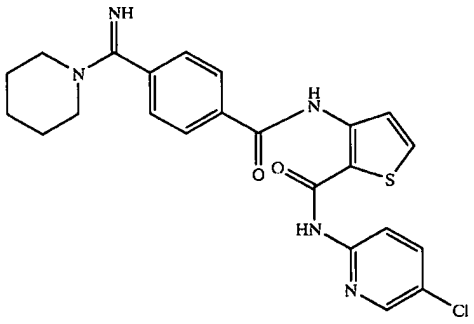
4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine



The title compound was obtained according to the procedure previously described. ES-MS 400(M+1).

Example 498

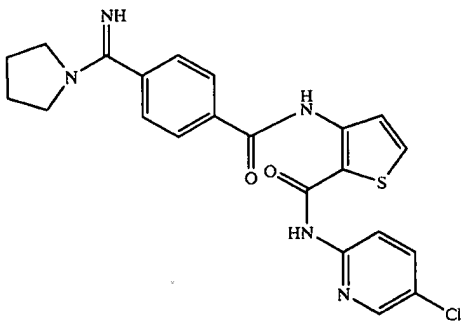
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)-phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 468(M+1).

Example 499

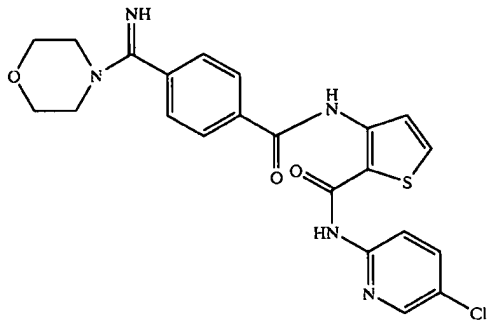
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidinylmethyl)-phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 454(M+1).

Example 500

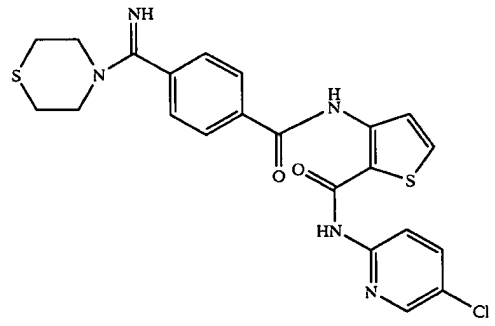
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}
[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 470(M+1).

Example 501

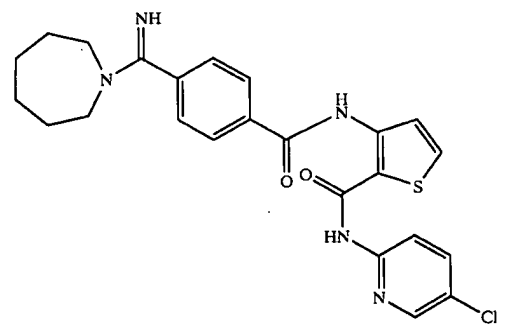
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}
[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]
carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 486(M+1).

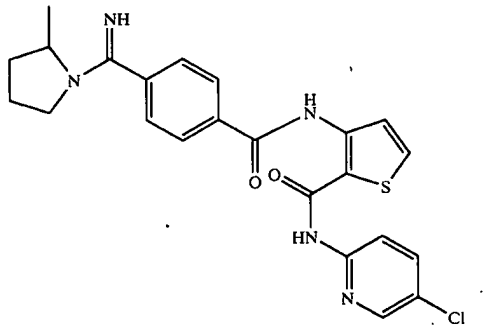
Example 502

[4-(azaperhydroepinyliminomethyl)phenyl]-N-{2-
[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}
carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 482(M+1).

Example 503

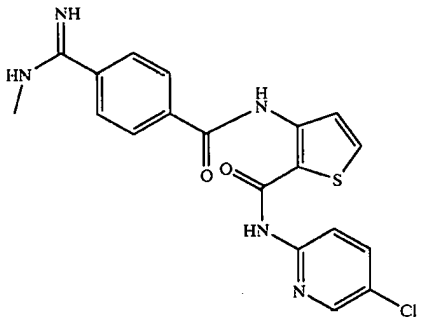


N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}
{4-[imino(2-methylpyrrolidinyl)methyl]
phenyl}carboxamide

The title compound was obtained according to the procedure previously described. ES-MS 468(M+1).

Example 504

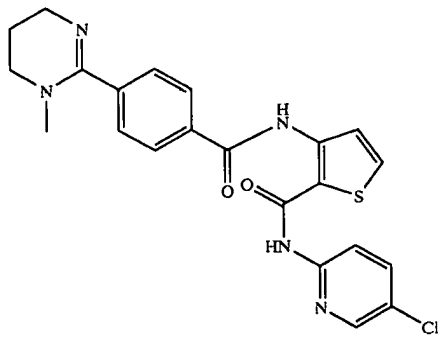
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}
{4-[imino(methylamino)methyl]-
phenyl}carboxamide



The title compound was obtained according to the procedure previously described.

Example 505

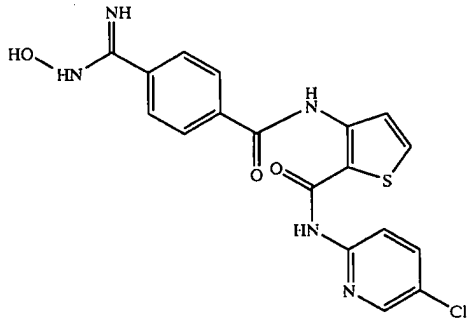
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}
[4-(3-methyl(3,4,5,6-tetrahydropyrimidin-2-yl))
phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 414(M+1).

Example 506

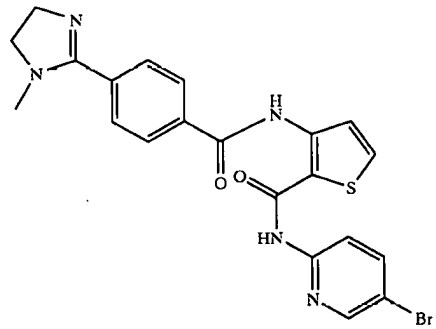
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}
[4-((hydroxyamino)iminomethyl)-phenyl]
carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 416(M+1).

Example 507

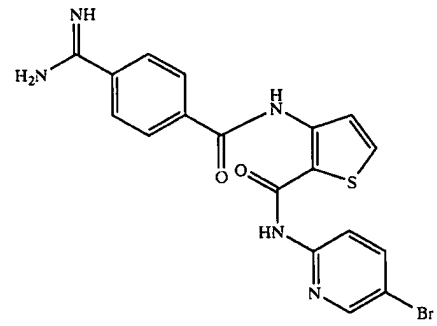
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}
[4-(1-methyl(2-imidazolin-2-yl))phenyl]
carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 484(M+1).

Example 508

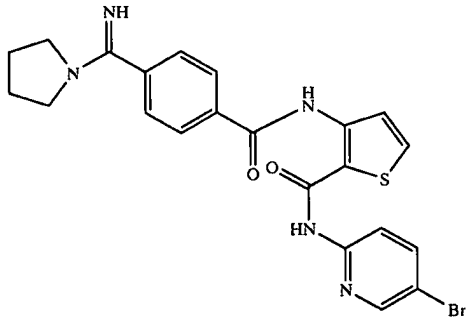
4-(N-{2-[N-(5-bromo-2-pyridyl)carbamoyl]-3-
thienyl}carbamoyl)benzenecarboxamidine



The title compound was obtained according to the procedure previously described. ES-MS 444(M+1).

Example 509

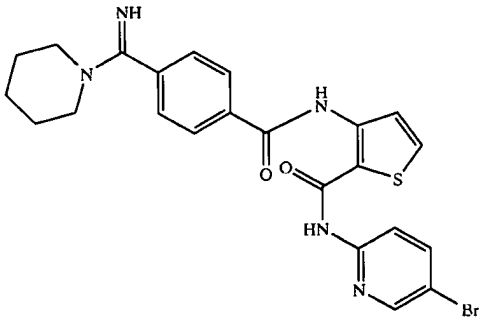
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}
[4-(iminopyrrolidinylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 494(M+1).

Example 510

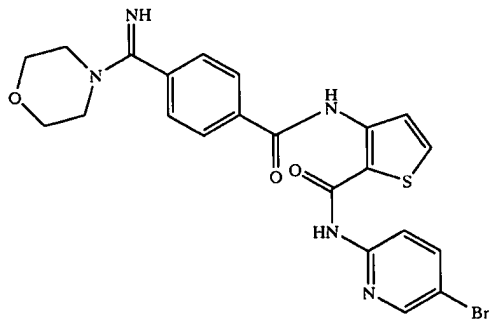
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}
[4-(iminopiperidylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 512(M+1).

Example 511

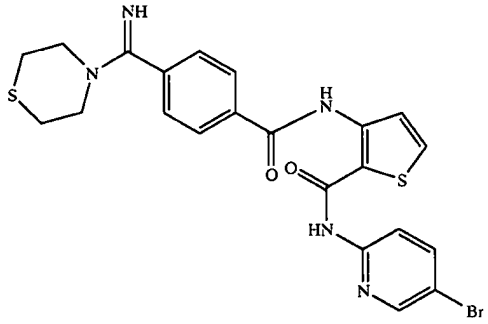
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}
[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 514(M+1).

Example 512

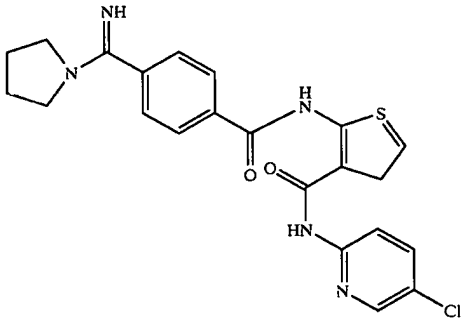
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}
[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]
carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 530(M+1).

Example 513

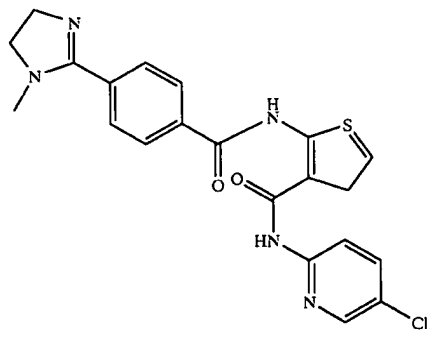
N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}
[4-(iminopyrrolidinylmethyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 454(M+1).

Example 514

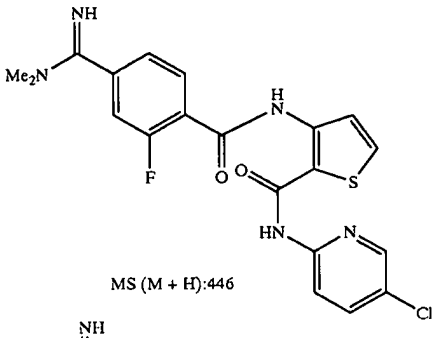
N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}
[4-(1-methyl(2-imidazolin-2-yl))phenyl]
carboxamide



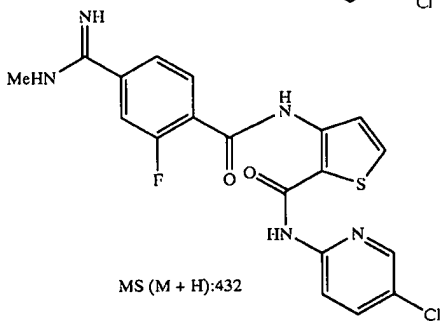
The title compound was obtained according to the procedure previously described. ES-MS 440(M+1).

Examples 515–520

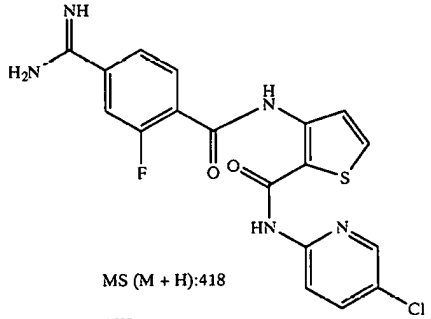
The following examples are prepared according to the procedure previously described.



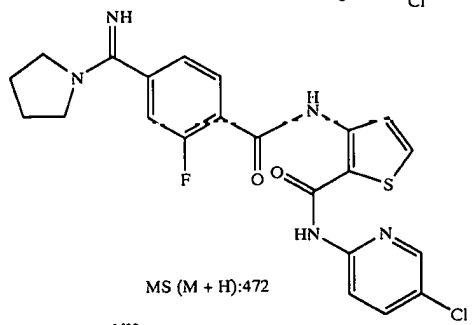
MS (M + H):446



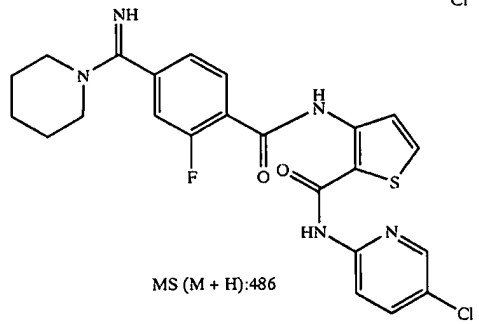
MS (M + H):432



MS (M + H):418



MS (M + H):472



MS (M + H):486

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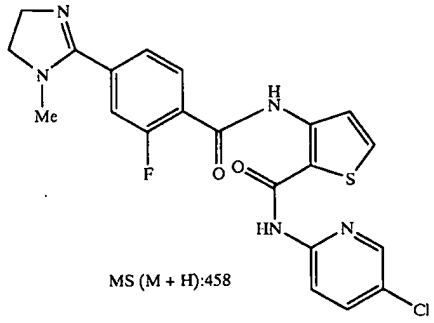
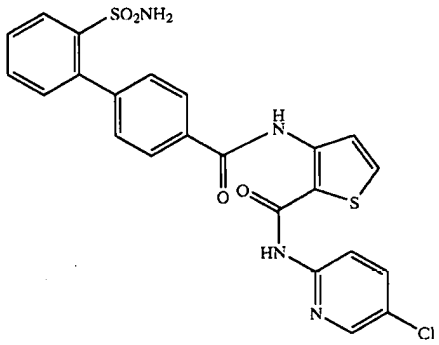


MS (M + H):458

Example 521

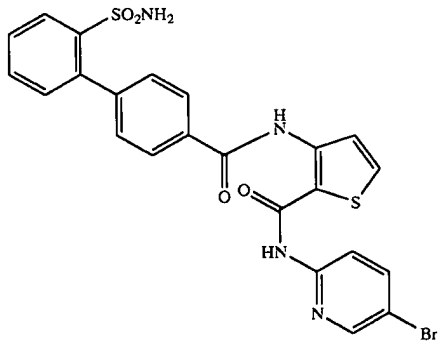
N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide



A solution of 4-(2-{[(tert-butyl)amino]sulfonyl}phenyl) benzoyl chloride (1 equiv), 3-amino-2-(4-chloro-2-pyridinyl)aminocarbonyl thiophene (1 equiv), pyridine (5 equiv) in dichloromethane was stirred at rt overnight. The mixture was diluted with dichloromethane, washed with water, dried over Na2SO4, filtered and evaporated. The residue was refluxed with 1 mL of TFA for 2 h. After evaporation, reverse phase HPLC gave the title product. ES-MS 513(M+1).

Example 522

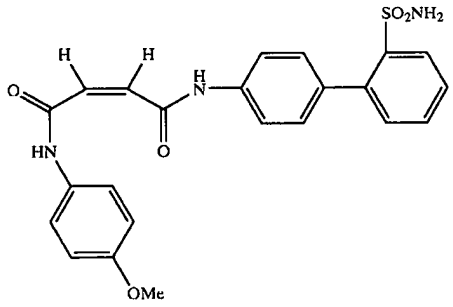
N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide



The title compound was obtained according to the procedure previously described. ES-MS 556(M+1).

Example 523

N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl) phenyl]phenyl)-maleamic amide



A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide.

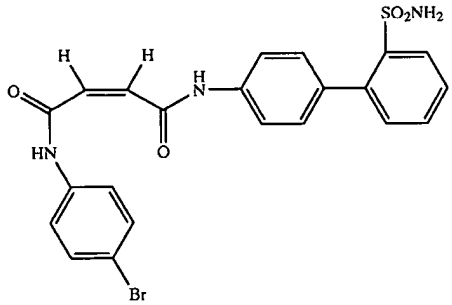
To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL), BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H_2O, then with 5% NaHCO3, dried over Na2SO4, concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH3CN in H2O (containing 0.1% TFA) to 100% CH3CN over 80 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (70 mg, yield: 31%). MS 508 (M+H).

B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl]phenyl)-maleamic amide (40 mg, 79 mol) was dissolved in TFA (3 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M+H) and 474 (M+Na). ^{1}H NMR (CDCl3) δ 11.40 (br.s, 1H), 10.28 (br.s, 1H), 8.12 (d, 1H, J=8 Hz), 7.72 (d, 2H, J=8 Hz), 7.60–7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 524

N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl] phenyl)-maleamic amide.



A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester.

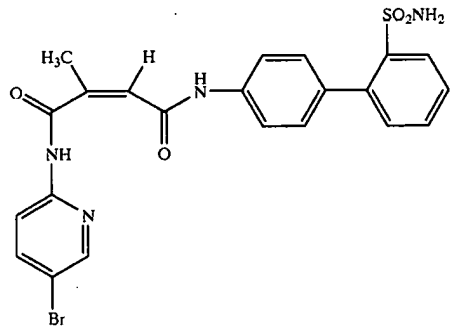
To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonylphenyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH2Cl2 (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH2Cl2 solution was then washed with sat. NaHCO3, 1N HCl and sat. NaCl. The solution was dried over Na2SO4, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10–40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M+H—^{t}Bu) and 439 (M+Na).

B. Preparation of N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH2Cl2 (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound N-(4-[(2-tert-butylaminosulfonyl) phenyl]phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2–3. Water and CH2Cl2 were added, and organic phase was separated, dried over Na2SO4, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M+H), 522 and 524 (M+Na). ^{1}H NMR (CD3OD) δ8.09 (d, 1H, J=8 Hz), 7.68 (d, 2H, J=8 Hz), 7.64–7.28 (m, 9H), 6.45 (AB type, 2H).

Examples 525 and 526

Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and $N^{1'}$-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl) phenyl]phenyl)-3-methylmaleamic amide.



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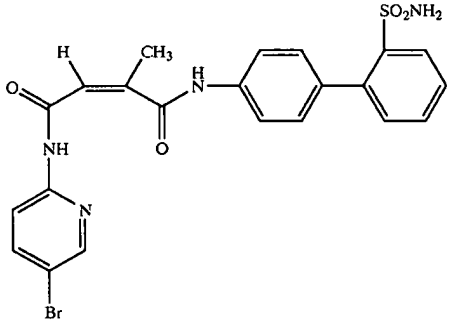


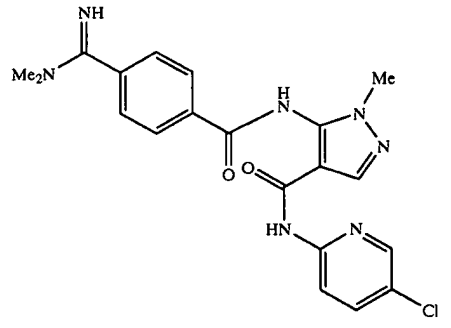
A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

A mixture of citraconic anhydride (1.00 mL, 11.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight. The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 (M+H).

B. Preparation of N^1-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and $N^{1'}$-(5-bromopyridin-2-yl)-N^4-(4-[(2-aminosulfonyl). phenyl]phenyl)-3-methylmaleamic amide.

To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH2Cl2 (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH2Cl2 (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2–3, which resulted in precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1:5. MS 515 and 517 (M+H), 537 and 539 (M+Na).

Example 527

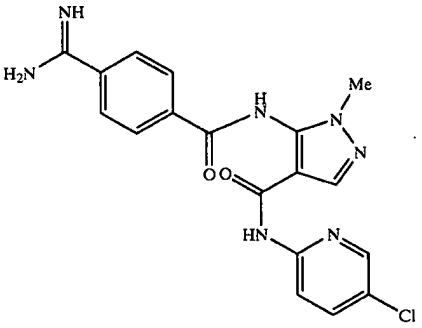


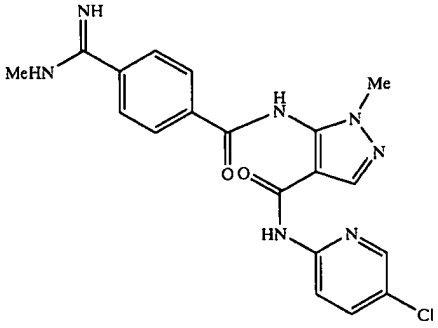
A solution of 3-amino-4-[(5-chloro-2-pyridinyl) aminocarbonyl]pyrazole (1 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 30 min. The resulting mixture was quenched by slow addition of water, and extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation, the residue was trituated with a small amount of CH_2Cl_2 and EtOAc. The solid on the glass

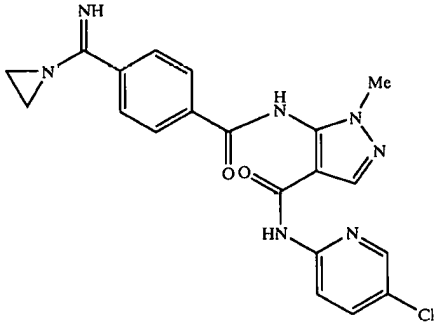
wall was then subjected to standard Pinner conditions to give desired product. MS $(M+H)^+$: 426.

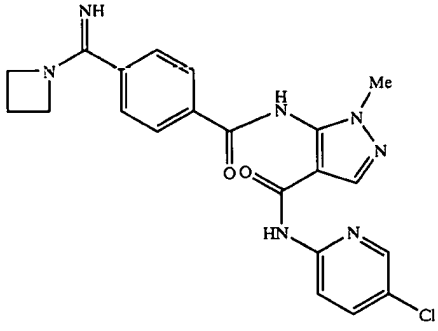
Examples 528–538

The following examples were prepared according to the procedure previously described.









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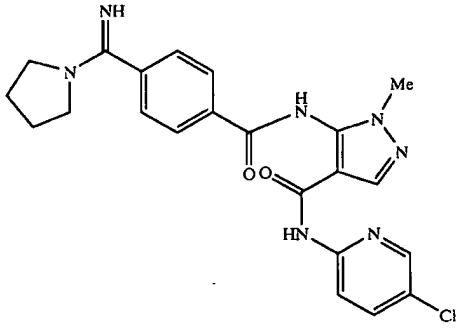

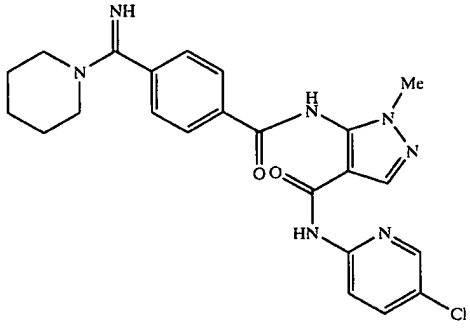

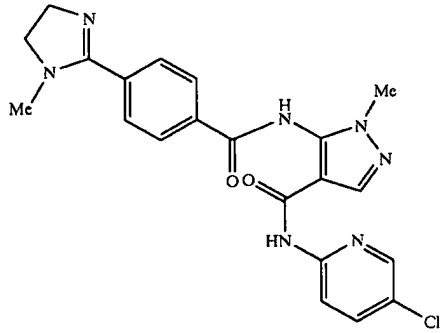

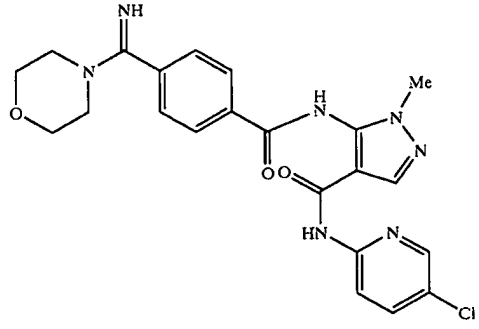

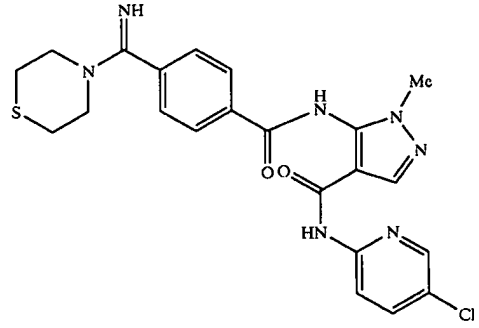

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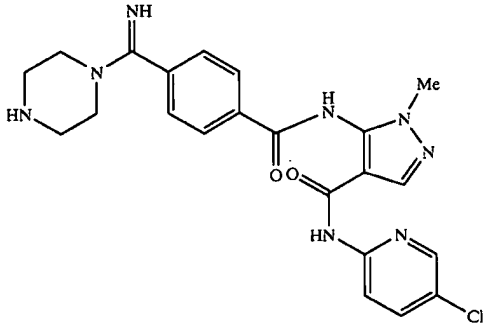
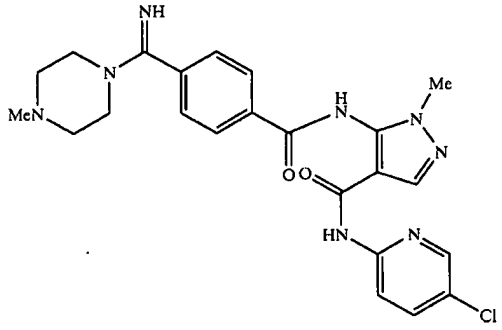
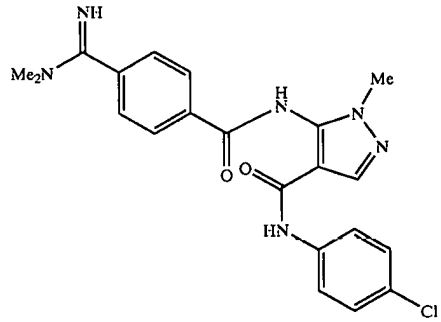




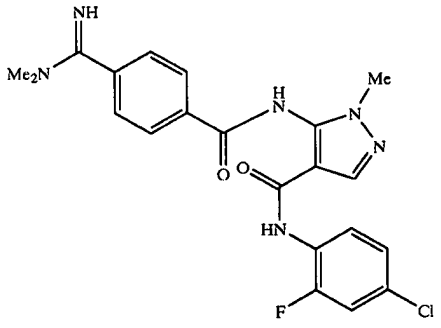
Example 539



Step 1: A solution of 3-amino-4-ethoxycarbonyl-pyrazole (3 equiv) and 4-cyanobenzoic acid (1 equiv) in pyridine was treated with $POCl_3$ (1.1 equiv) for 1 h. The resulting mixture was quenched by slow addition of water, extracted with CH_2Cl_2, dried over $MgSO_4$, and purified by column chromatography to give the desired product.

Step 2: The compound obtained in step 1 (1 equiv) in DMF was treated with NaSMe (10 equiv) at 65° C. overnight. The resulting mixture was quenched by slow addition of water, and acidified with 1 N HCl, extracted with EtOAc, and dried over $MgSO_4$The acid was reflux in excess $SOCl_2$ for 2 h. The volatile was removed on rotovap, and the residue was redissolved in pyridine, refluxed overnight in the presence of DMAP (1 equiv) and 4-chloroaniline (10 equiv). The resulting mixture was quenched by slow addition of water, and extracted with CH_2Cl_2 and dried over $MgSO_4$. After evaporation, the residue was trituated with a small amount of CH_2Cl_2 and EtOAc. The solid on the glass wall was then subjected to standard Pinner conditions to give desired product. MS $(M+H)^+$: 425.

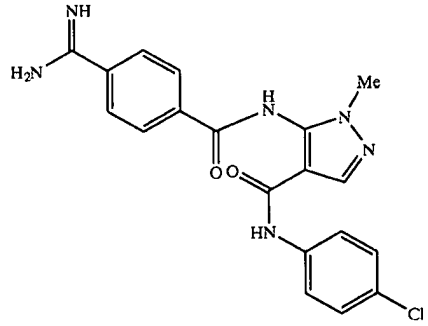
Example 540

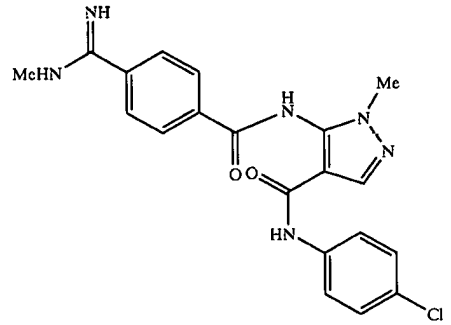


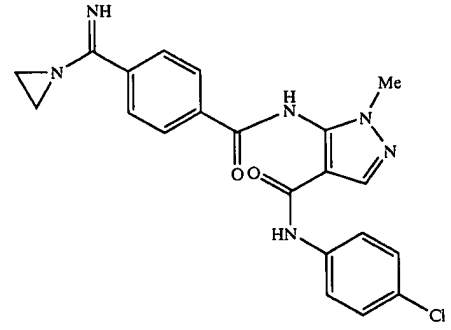
Similarly prepared as Example 350. MS $(M+H)^+$: 443.

Examples 541–551

The following examples were prepared according to the procedure previously described.







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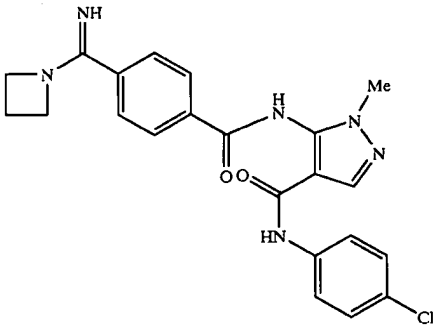

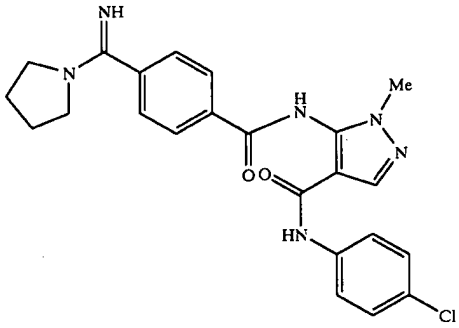

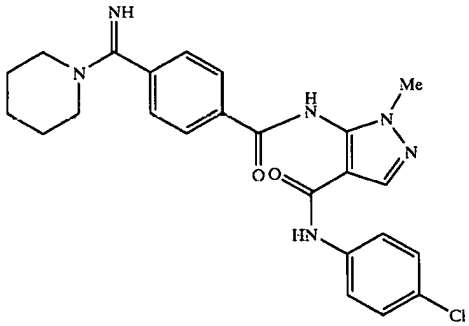

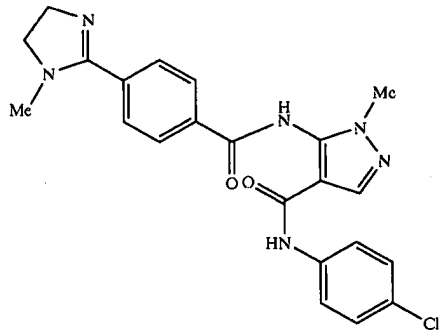

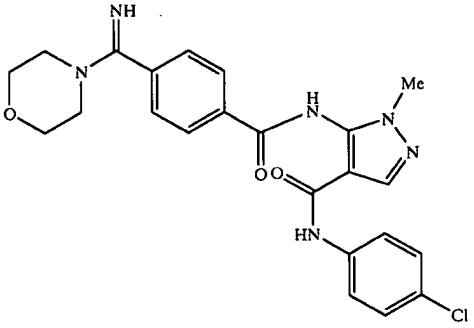

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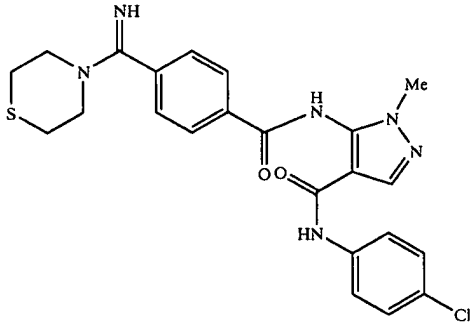
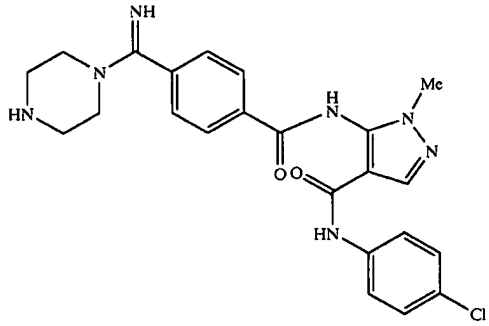
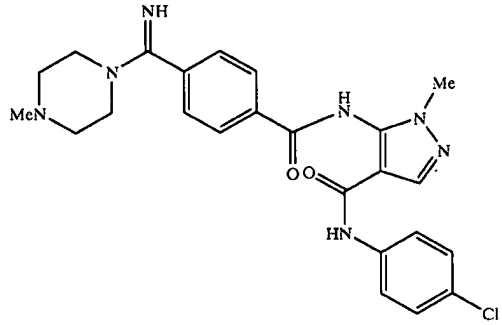
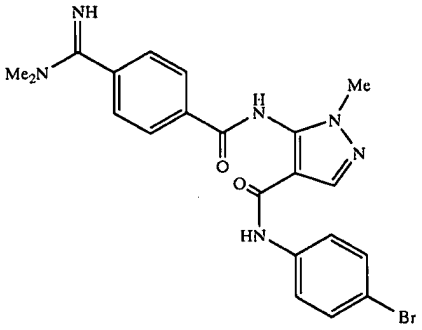






Examples 552–559

The following examples were prepared according to the procedure previously described.



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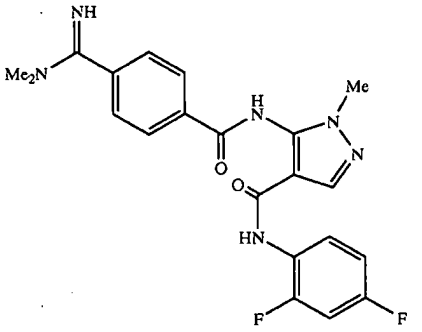

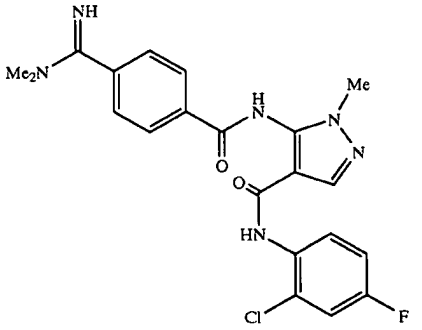

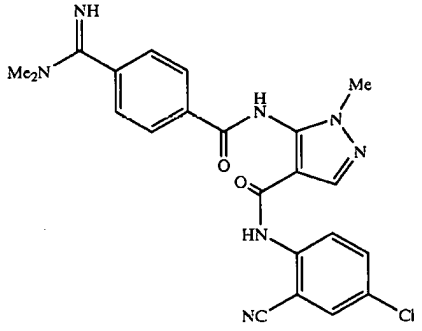

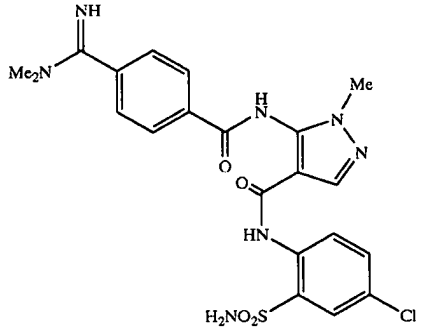

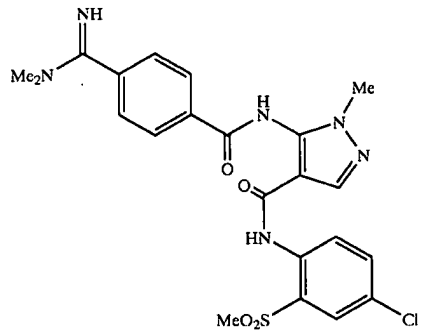

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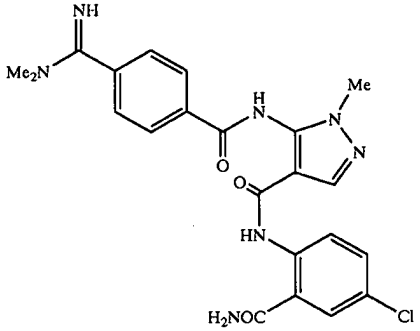
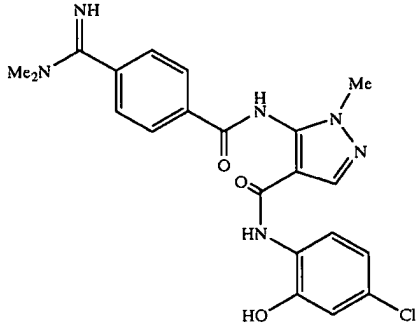
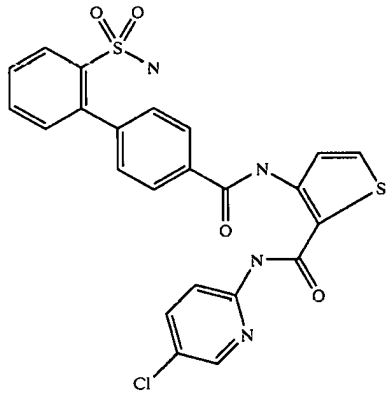


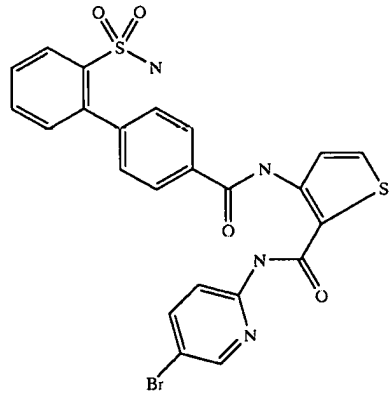


Example 560



The title compound was synthesized according to the procedure described previously. ES-MS 514(M+1).

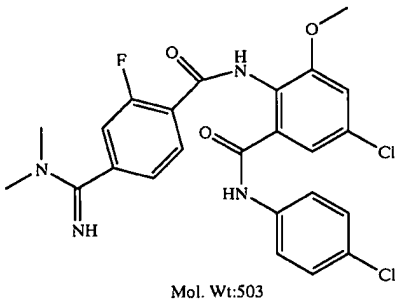
Example 561



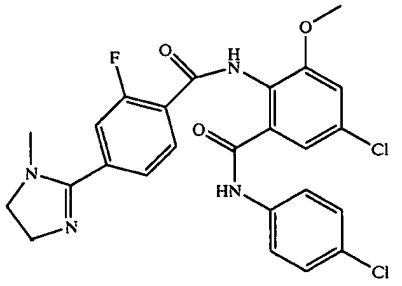
The title compound was synthesized according to the procedure described previously. ES-MS 558(M+1).

Example 562–585

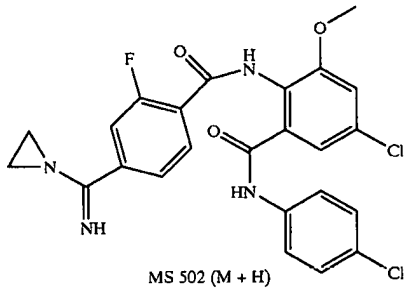
The following compounds were prepared according to the procedure previously described.



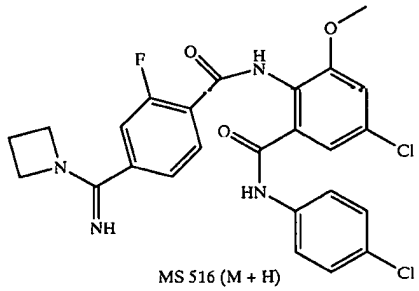
Mol. Wt:503



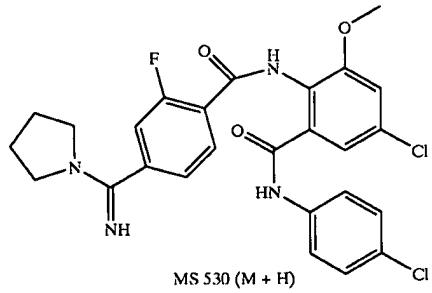
Mol. Wt:515



MS 502 (M + H)

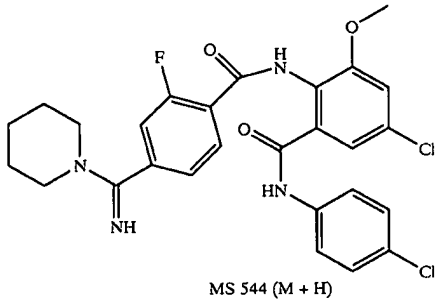


MS 516 (M + H)

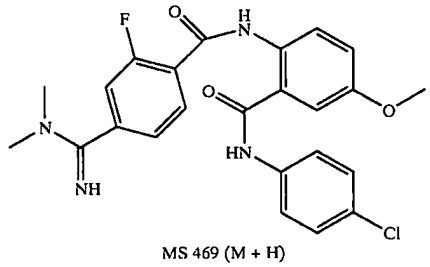


MS 530 (M + H)

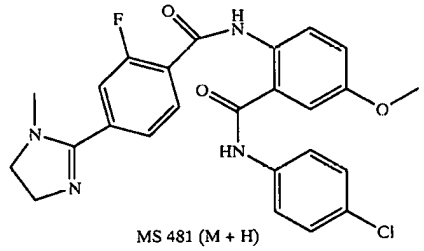
-continued



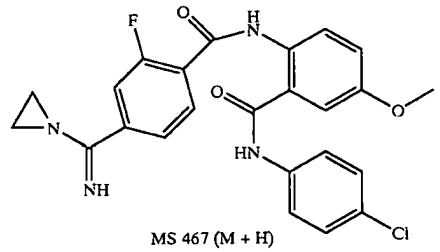
MS 544 (M + H)



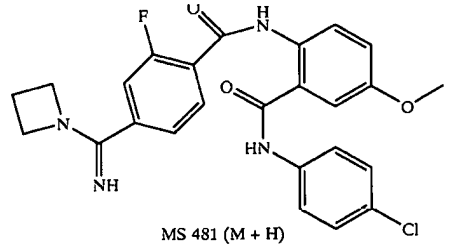
MS 469 (M + H)



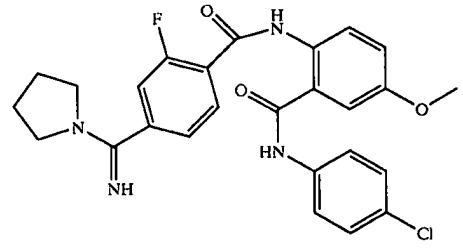
MS 481 (M + H)



MS 467 (M + H)

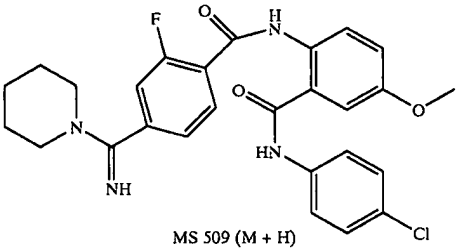


MS 481 (M + H)

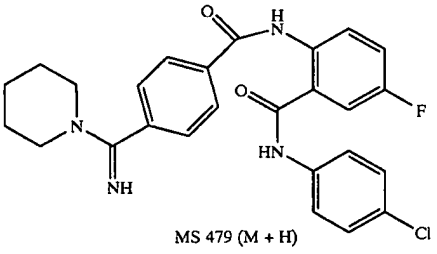


MS 495 (M + H)

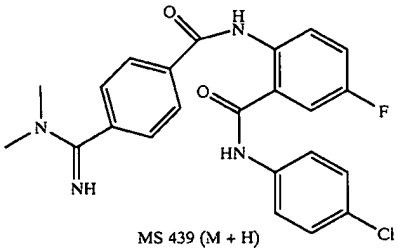
-continued



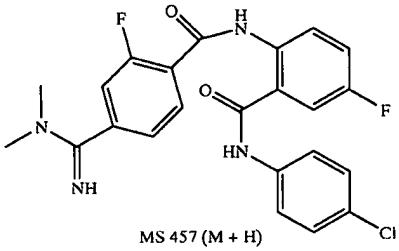
MS 509 (M + H)



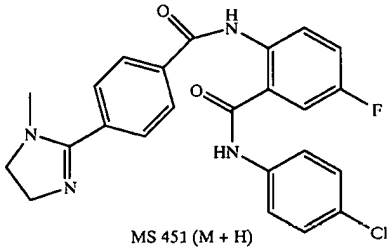
MS 479 (M + H)



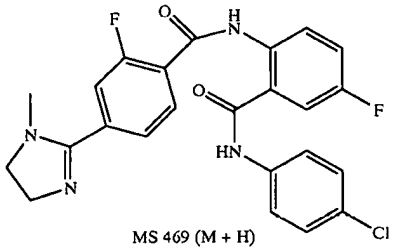
MS 439 (M + H)



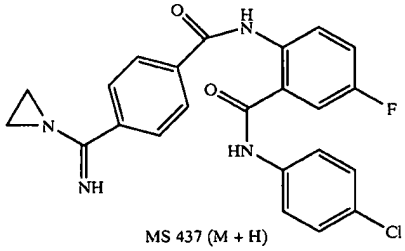
MS 457 (M + H)



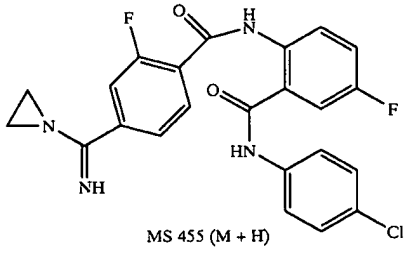
MS 451 (M + H)



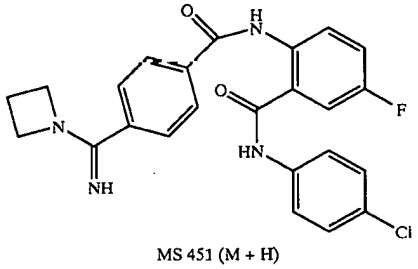
MS 469 (M + H)



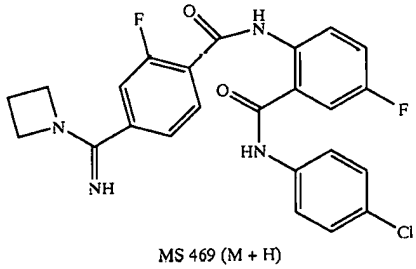
MS 437 (M + H)



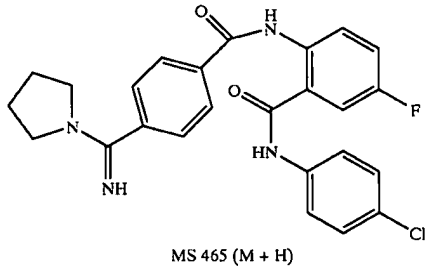
MS 455 (M + H)



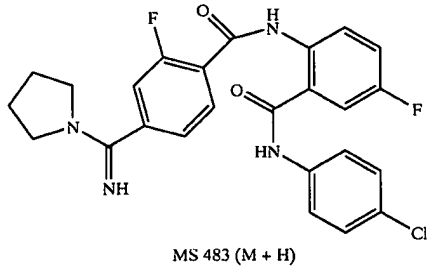
MS 451 (M + H)



MS 469 (M + H)

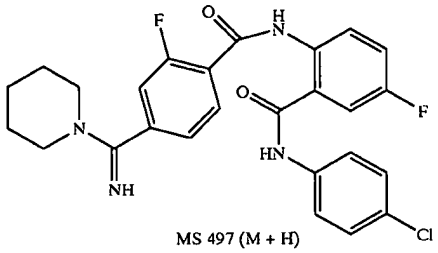


MS 465 (M + H)



MS 483 (M + H)

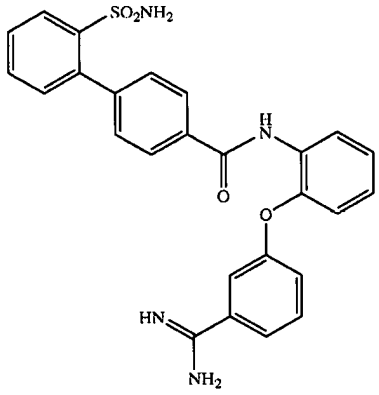
-continued



MS 497 (M + H)

Example 586

3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine.



Step 1: To a solution of 2-fluoro nitrobenzene (1.41 g, 10 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (1.19 g, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (2.76 g, 2 equiv). After stirring at 60° C. for 3 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-nitrophenoxy)benzonitrile (2.38 g, 99%). MS found for $C_{13}H_9N_2O_3$ $(M+H)^+$: 241.

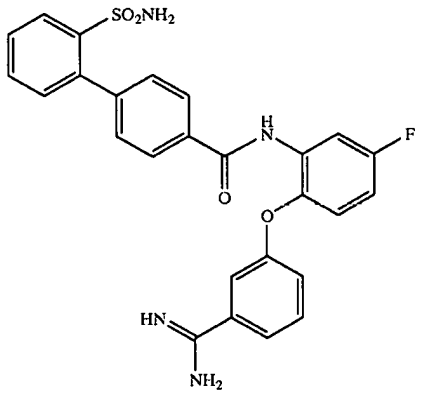
Step 2: A solution of 3-(2-nitrophenoxy)benzonitrile (1.21 g, 5 mmol, 1.0 equiv) in 30 mL of EtOH was treated with $SnCl_2.2H_2O$ (3.38 g, 3 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-aminophenoxy)benzonitrile (1.04 g, 99%). MS found for $C_{13}H_{11}N_2O$ $(M+H)^+$: 211.

Step 3: A mixture of 3-(2-aminophenoxy)benzonitrile (210 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl) phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) benzonitrile (300 mg, 57%). MS found for $C_{30}H_{28}N_3O_4S$ $(M+H)^+$: 526.

Step 4: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] benzoylamino)phenoxy)benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine (40 mg, 83%). MS found for $C_{26}H_{23}N_4O_4S$ $(M+H)^+$: 487.

Example 587

3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) benzamidine.

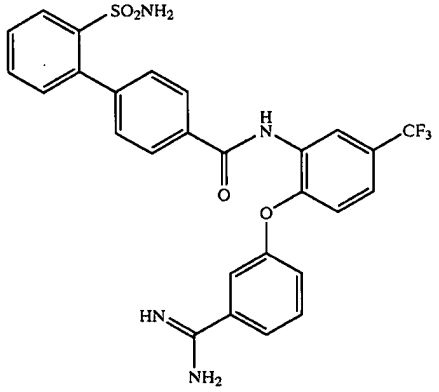


Step 1: A mixture of 3-(2-amino-4-fluorophenoxy) benzonitrile (230 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (495 mg, 91%). MS found for $C_{30}H_{27}FN_3O_4S$ $(M+H)^+$: 544.

Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl) phenyl]phenylcarbonylamino)phenoxy) benzonitrile (55 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (39 mg, 77%). MS found for $C_{26}H_{22}FN_4O_4S$ $(M+H)^+$: 505.

Example 588

3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) benzamidine.

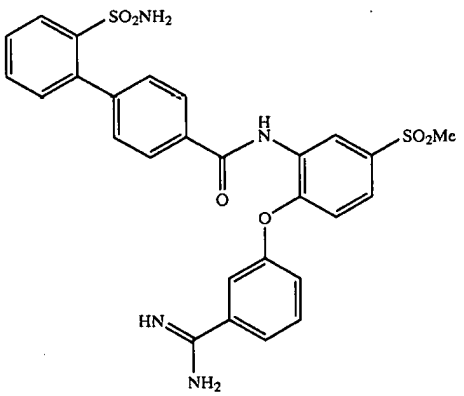


Step 1: A mixture of 3-(2-amino-^{4}-trifluoromethylphenoxy) benzonitrile (280 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) benzonitrile (529 mg, 89%). MS found for $C_{31}H_{27}F_3N_3O_4S$ $(M+H)^+$: 594.

Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (59 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified. by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (35 mg, 63%). MS found for $C_{27}H_{22}F_3N_4O_4S$ $(M+H)^+$: 555.

Example 589

3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) benzamidine.

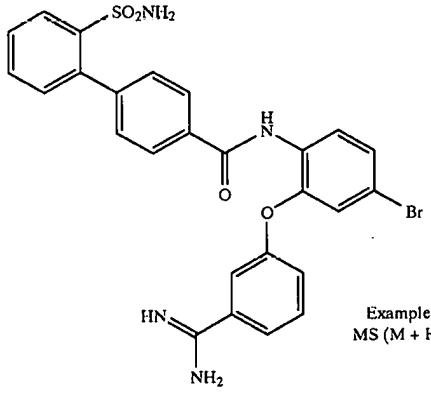


Step 1: A mixture of 3-(2-amino-4-methylsulfonylphenoxy) benzonitrile (290 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) benzonitrile (429 mg, 71%). MS found for $C_{31}H_{30}N_3O_6S_2$ $(M+H)^+$: 604.

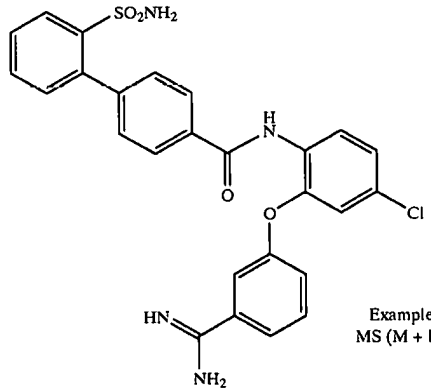
Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (60 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (27 mg, 47%). MS found for $C_{27}H_{25}N_4O_6S_2$ $(M+H)^+$: 565.

Examples 590–593

The following compounds were prepared using the procedure previously described.

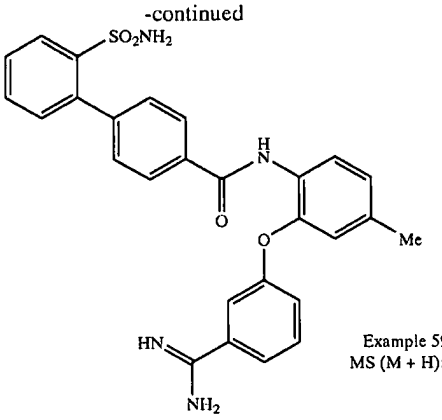


Example 590
MS (M + H):565

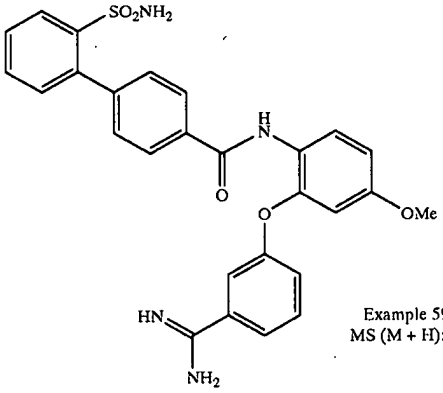


Example 591
MS (M + H):521

-continued



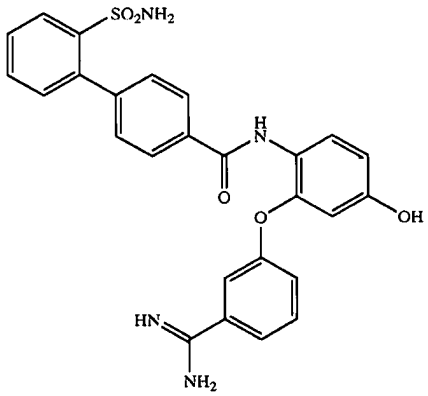
Example 592
MS (M + H):501



Example 593
MS (M + H):517

Example 594

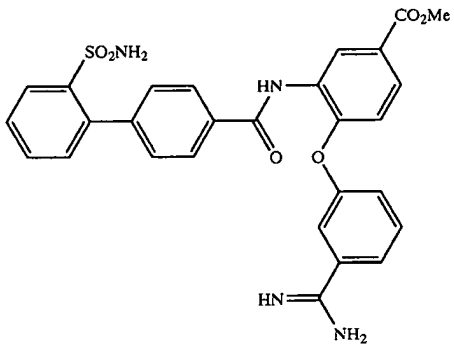
3-(5-hydroxy-2-(4-[(2-aminosulfonyl) phenyl] phenylcarbonylamino)phenoxy) benzamidine.



A solution of 3-(5-methoxy-2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino) phenoxy) benzamidine (52 mg, 0.1 mmol, 1 equiv) in 5 mL of methylene chloride was treated with BBr_3 (1 M in dichloromethane, 0.5 mL, 5 equiv) overnight. The reaction was quenched with water carefully and after the volatile was evaporated, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine. (41 mg, 82%). MS found for $C_{26}H_{23}N_4O_6S$ $(M+H)^+$: 503.

Example 595

3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)phenoxy) benzamidine.

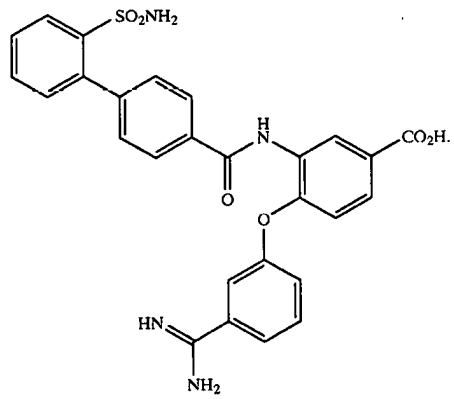


Step 1: A mixture of 3-(2-amino-4-methoxycarbonyl-phenoxy)benzonitrile (270 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) benzonitrile (502 mg, 86%). MS found for $C_{32}H_{30}N_3O_6S$ $(M+H)^+$: 584.

Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (58 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (29.5 mg, 54%). MS found for $C_{28}H_{25}N_4O_6S$ $(M+H)^+$: 545.

Example 596

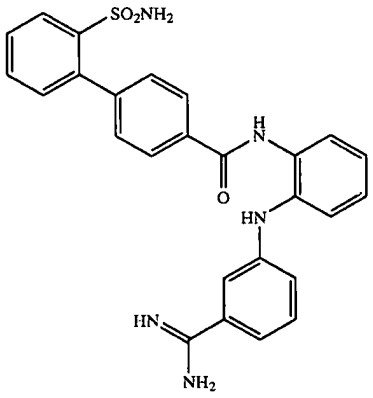
3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl) phenyl]phenylcarbonylamino)phenoxy) benzamidine.



A solution of 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (10.9 mg, 0.02 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) benzamidine (8.9 mg, 84%). MS found for $C_{27}H_{23}N_4O_6S$ $(M+H)^+$: 531.

Example 597

3-(2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenylamino) benzamidine.

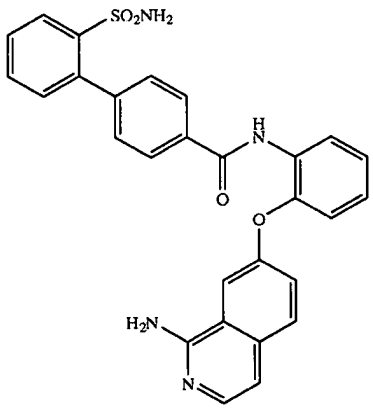


Step 1: A mixture of 3-(2-amino-phenylamino)benzonitrile (196 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl) phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl) phenyl]phenylcarbonylamino) phenylamino) benzonitrile (226 mg, 43%). MS found for $C_{30}H_{29}N_4O_3S$ $(M+H)^+$: 525.

Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino)phenylamino) benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino) phenylamino) benzamidine (27 mg, 55%). MS found for $C_{26}H_{24}N_5O_3S$ $(M+H)^+$: 486.

Example 598

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)-1-aminoisoquinoline.

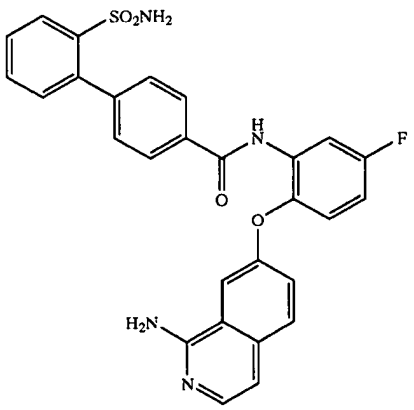


Step 1: A mixture of 7-(2-aminophenoxy)isoquinoline (237 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl) phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) isoquinoline (469 mg, 85%). MS found for $C_{32}H_{30}N_3O_4S$ $(M+H)^+$: 552.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl) phenyl]benzoylamino)phenoxy) isoquinoline (110 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with mCPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 2 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl] benzoylamino)phenoxy)-1-aminoisoquinoline (43 mg, 42%). MS found for $C_{28}H_{23}N_4O_4S$ $(M+H)^+$: 511.

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) 1-aminoisoquinoline.

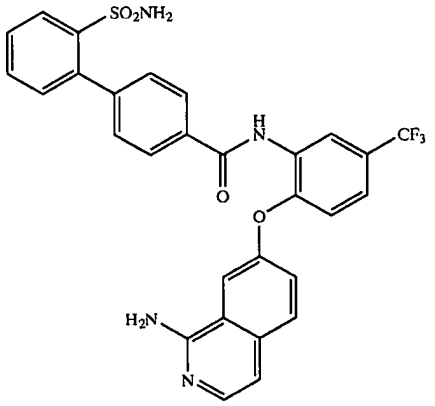


Step 1: A mixture of 7-(2-amino-4-fluorophenoxy) isoquinoline (255 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (467 mg, 82%). MS found for $C_{32}H_{29}FN_3O_4S$ $(M+H)^+$: 570.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl) phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (114, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with mCPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl] benzoylamino)-4-fluorophenoxy)1-aminoisoquinoline (77 mg, 50%). MS found for $C_{28}H_{22}FN_4O_4S$ $(M+H)^+$: 529.

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline.



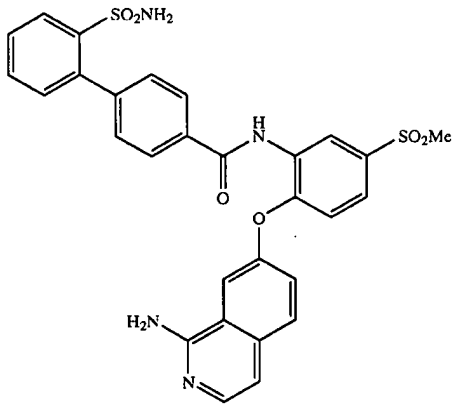
Step 1: A mixture of 7-(2-amino-4-trifluoromethylphenoxy) isoquinoline (305 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (360 mg, 58%). MS found for $C_{33}H_{29}F_3N_3O_4S$. $(M+H)^+$:620.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl) phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (124 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with mCPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated. the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and used in the next step directly.

Step3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl] benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline (64 mg, 52%). MS found for $C_{29}H_{22}F_3N_4O_4S$ $(M+H)^+$: 579.

Example 601

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline.



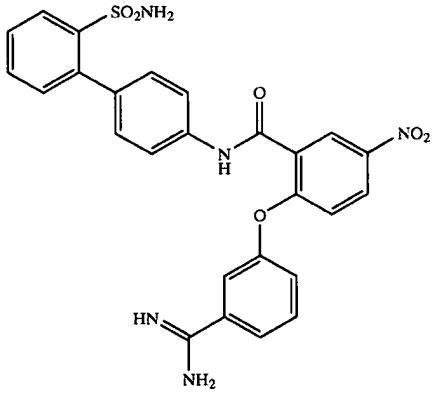
Step 1: A mixture of 7-(2-amino-4-methylsulfonylphenoxy) isoquinoline (315 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methlsulfonylphenoxy) isoquinoline (460 mg, 73%). MS found for $C_{33}H_{32}N_3O_6S_2$ $(M+H)^+$: 630.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl) phenyl]benzoylamino)-4-methlsulfonylphenoxy) isoquinoline (126 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with mCPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried over $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl] benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline (94 mg, 80%). MS found for $C_{29}H_{25}N_4O_6S_2$ $(M+H)^+$: 589.

Example 602

3-(2-(4-[(2-aminosulfonyl)phenyl] phenylaminocarbonyl-4-nitrophenoxy) benzamidine.



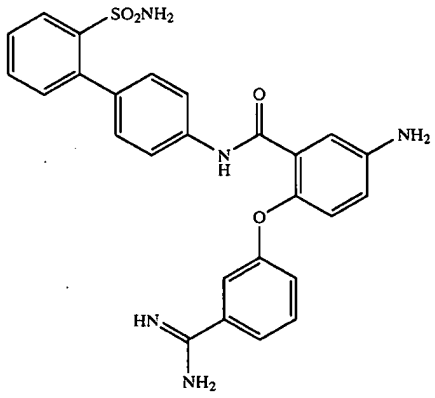
Step 1: A solution of 2-fluoro-5-nitrobenzoic acid (1.85 g, 10 mmol, 1.33 equiv) in thionyl chloride (5 mL) was refluxed for 2 h and evaporated. The residue was redissolved in 20 mL of methylene chloride and to the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]aniline (2.0 g, 1.0 equiv) and 5 mL of pyridine. After stirring at rt overnight, the volatile was evaporated. Flash chromatography on silica gel 1-(4-[(2-t-butylaminosulfonyl)phenyl] phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (2.9 g, 99%). MS found for $C_{23}H_{23}FN_3O_5S$ $(M+H)^+$: 472.

Step 2: To a solution of 1-(4-[(2-t-butylaminosulfonyl) phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (1.18 g, 0.25 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (298 mg, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (691 mg, 2 equiv). After stirring at 60° C. for 3 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and chromatographied to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile(950 g, 63%). MS found for $C_{30}H_{27}N_4O_6S$ $(M+H)^+$: 571.

Step 3: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (57 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine (24 mg, 45%). MS found for $C_{26}H_{22}N_5O_6S$ $(M+H)^+$: 532.

Example 603

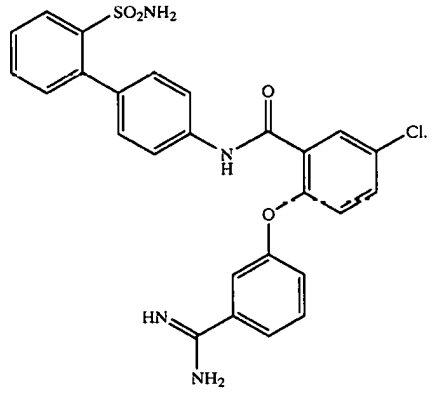
3-(2-(4-[(2-aminosulfonyl)phenyl] phenylaminocarbonyl-4-aminophenoxy) benzamidine.



A mixture of 3-(2-(4-[(2-aminosulfonyl)phenyl] phenylaminocarbonyl-4-nitrophenoxy) benzamidine (53 mg, 0.1 mmol, 1 equiv), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl) phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine (31 mg, 66%). MS found for $C_{26}H_{24}N_5O_4S$ $(M+H)^+$: 502.

Example 604

3-(2-(4-[(2-aminosulfonyl)phenyl] phenylaminocarbonyl-4-chlorophenoxy) benzamidine.



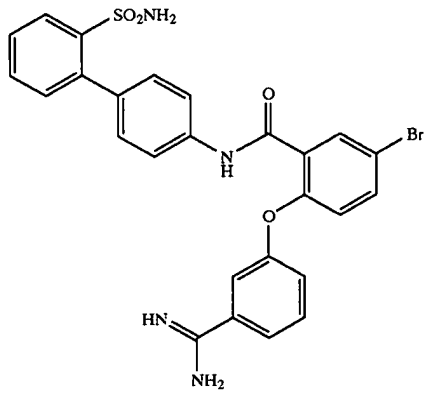
Step 1: A mixture of 3-(2-(4-[(2-t-butylaminosulfonyl) phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (570 mg, 1 mmol, 1 equiv) and $SnCl_2.2H_2O$ (677 mg, 3 equiv) in 25 mL of EtOAc was refluxed for 2 h. The reaction was quenched with sat. $NaHCO_3$. The organic layer was separated and dried over $MgSO_4$, filtered and evaporated to give 3-(2-(4-[(2-t-butylaminosulfonyl) phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (45 mg, 83%). MS found for $C_{30}H_{29}N_4O_4S$ $(M+H)^+$: 541.

Step 2: A mixture of t-$BuNO_2$ (21 mg, 0.1 mmol, 2 equiv), CuCl (20 mg, 2 equiv) in 5 mL of acetonitrile was refluxed for 10 min. To the solution was added 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (54 mg, 0.1 mmol, 1 equiv). The mixture was refluxed for 1 h and evaporated. Flash chromatography with 1:2 EtOAc/hexane to give [(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (43 mg, 77%)MS found for $C_{30}H_{27}ClN_3O_4S$ $(M+H)^+$: 561.

Step 3: A stream of HCl(g) was bubbled through a 0° C. solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (56 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzamidine (47 mg, 84%). MS found for $C_{20}H_{22}ClN_4O_4S$ $(M+H)^+$: 521.

Example 605

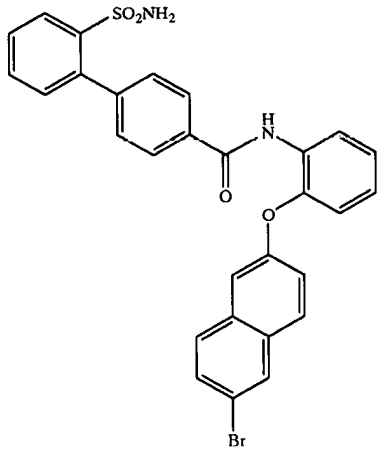
3-(2-(4-[(2-aminosulfonyl)phenyl] phenylaminocarbonyl-4-bromophenoxy) benzamidine.



This compound was prepared according to the procedure described in example 19. MS found for $C_{26}H_{22}BrN_4O_4S$ $(M+H)^+$: 565.

Example 606

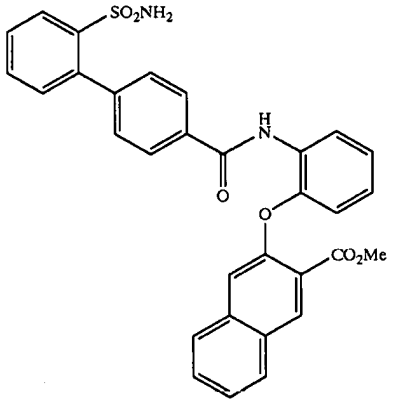
2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy naphthalene.



A mixture of 2-bromo-6-(2-aminophenoxy) naphthalene (314 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl) phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (378 mg, 66%). MS found for $C_{29}H_{22}BrN_2O_4S$ $(M+H)^+$: 573.

Example 607

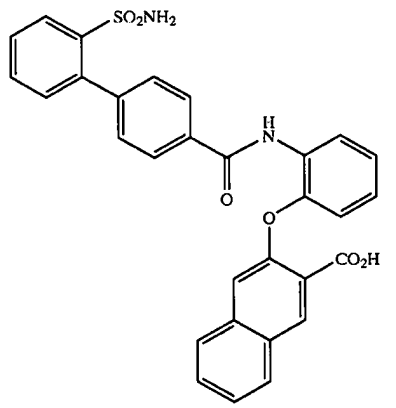
3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy naphthalene.



A mixture of 3-methoxycarbonyl-2-(2-aminophenoxy) (294 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl] benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy naphthalene (420 mg, 76%). MS found for $C_{31}H_{25}N_2O_6S$ $(M+H)^+$: 553.

Example 608

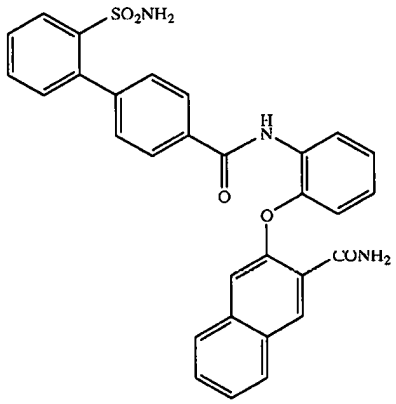
3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy naphthalene.



A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (55 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy naphthalene (47 mg, 88%). MS found for $C_{30}H_{23}N_2O_6S$ $(M+H)^+$: 539.

Example 609

3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy naphthalene.

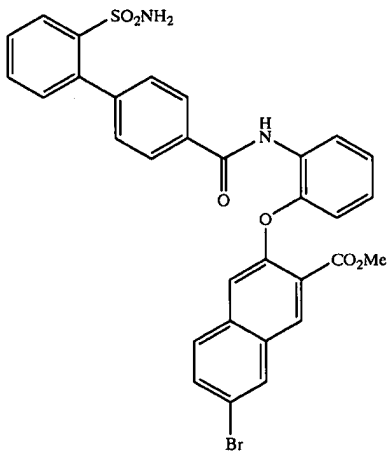


Step 1: A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) naphthalene (40 mg, 0.066 mmol) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, and acidified with 1N HCl until PH~1–2. The product (39 mg, 100%), 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino) phenoxy) naphthalene, was extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated. MS found for $C_{34}H_{31}NO_6S$ $(M+H)^+$: 595.

Step 2: A solution of 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl] phenylcarbonylamino)phenoxy) naphthalene (39 mg, 0.066 mmol) was refluxed in 3 mL of thionyl chloride for 2 h and evaporated. The residue was then stirred in 5 mL of 2M ammonia in methanol overnight. The volatile was evaporated and the residue was refluxed in 2 mL of trifluoroacetic acid overnight to give the product 3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy naphthalene (14 mg, 39%) after HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN). MS found for $C_{30}H_{24}N_3O_5S$ $(M+H)^+$: 538.

Example 610

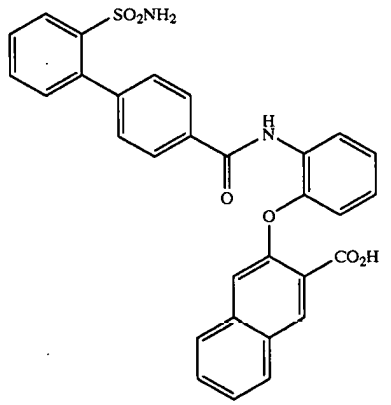
3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy-6-bromo naphthalene.



A mixture of 2-(2-aminophenoxy)-3-methoxycarbonyl-6-bromo naphthalene (372 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (423 mg, 67%). MS found for $C_{31}H_{24}BrN_2O6S$ $(M+H)^+$: 631.

Example 611

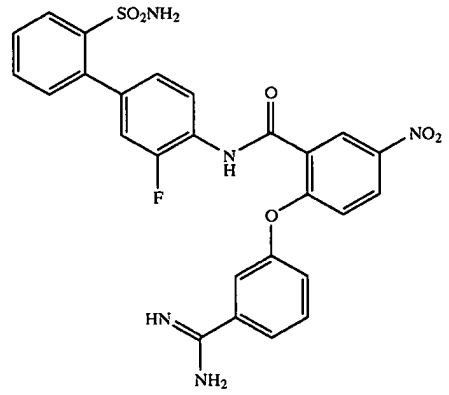
3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy-6-bromo naphthalene.



A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy)-6-bromo naphthalene (63 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)phenoxy-6-bromo naphthalene (47 mg, 78%). MS found for $C_{30}H_{22}BrN_2O6S$ $(M+H)^+$: 617.

Example 612

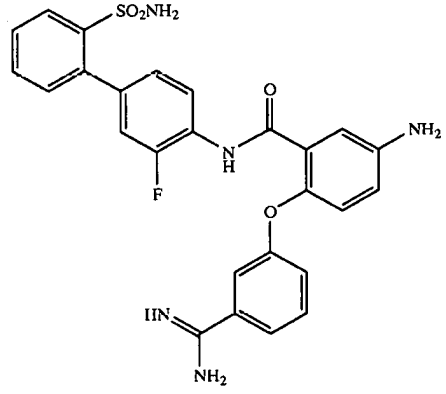
3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine.



This compound was prepared according to the procedure described in example 17. MS found for MS found for $C_{26}H_{21}FN_5O_6S$ $(M+H)^+$: 550.

Example 613

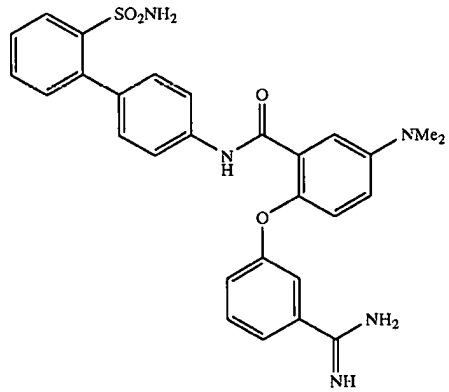
3-(2-(4-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzamidine.



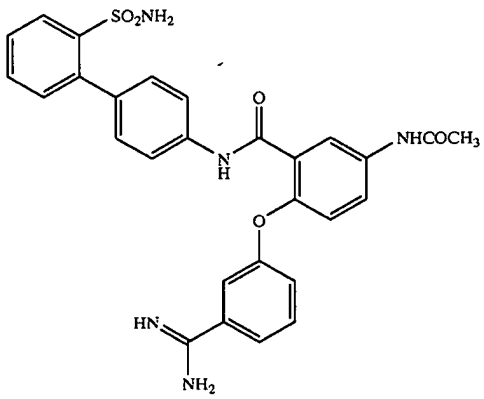
This compound was prepared according to the procedure described in example 18. MS found for $C_{26}H_{23}FN_5O_4S$ $(M+H)^+$: 520.

Example 614

This compound was obtained as a side product in the preparation of example 18. MS $(M+H)^+$: 530.



Example 615

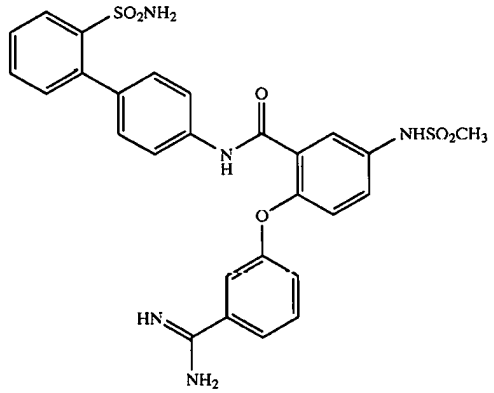


Step 1: A mixture of 3-(2-(4-[(2-t-butylaminosulfonyl) phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (1 equiv) and $SnCl_2$ $2H_2O$ (3 equiv) in 15 mL of EtOAc was refluxed for 2 h. The mixture was diluted with EtOAc and washed with saturated aqueous NaHCO3. The organic layer was dried over Na2SO4, filtered and evaporated.

Step 2: The product obtained in step 1 (1 equiv) in 2 mL of pyridine was treated with AcCl (1 equiv) over night. The mixture was diluted with methylene chloride and washed with water. The organic layer was dried over Na_2SO_4, filtered and evaporated.

Step 3: A stream of HCl(g) was bubbled through a 0° C. solution of the product obtained in step 2 (1 equiv) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to the title product. MS $(M+H)^+$: 544.

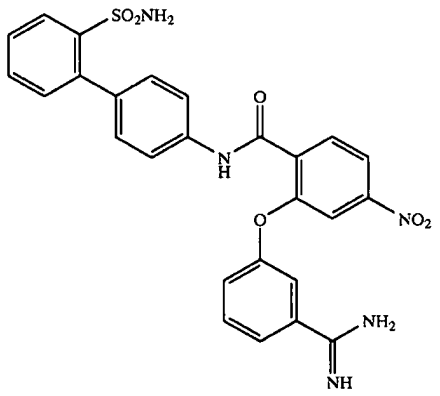
Example 616

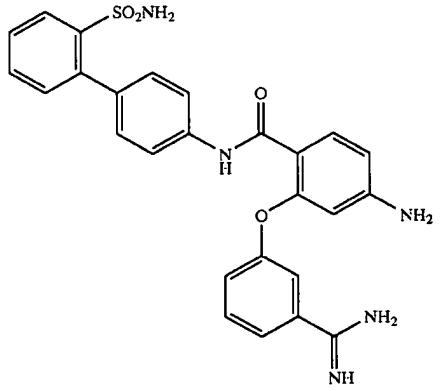


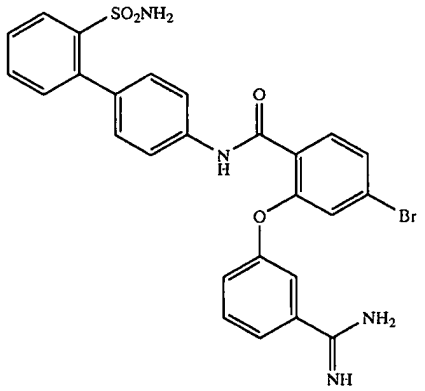
This compound was similarly made as example 30. MS $(M+H)^+$: 580.

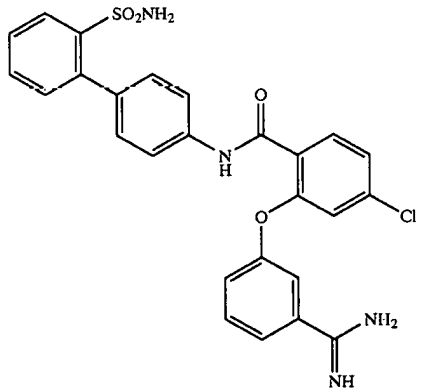
Examples 617–624

The following compounds were made according to the methods previously described.









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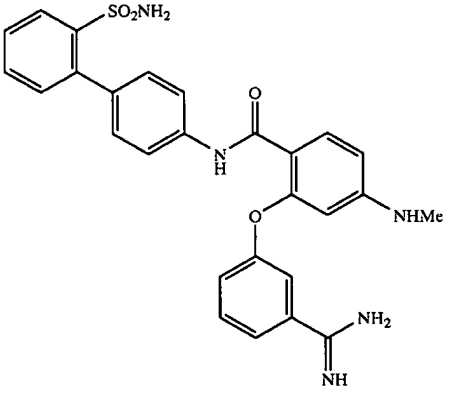
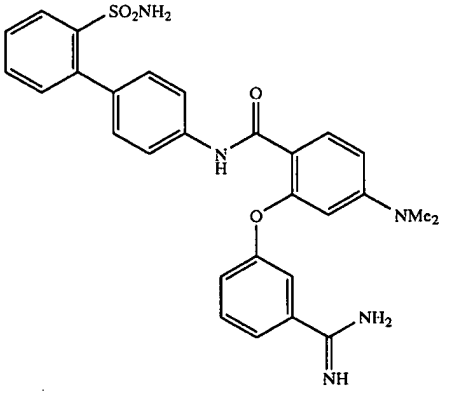
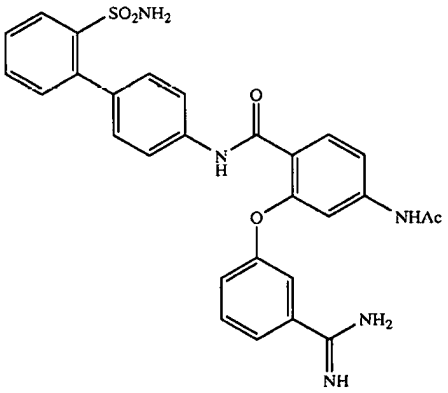
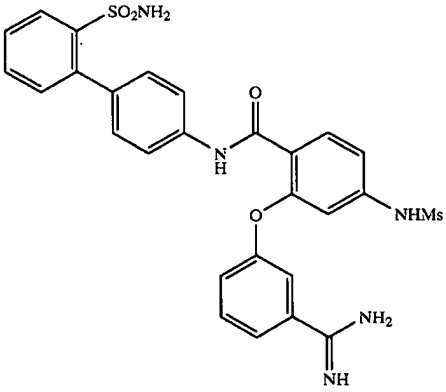
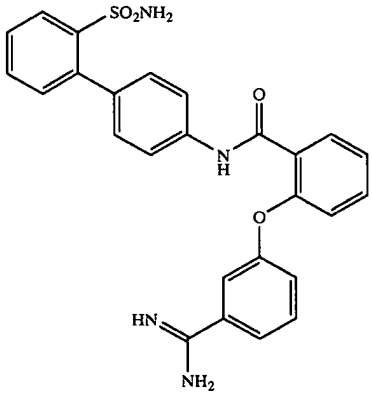








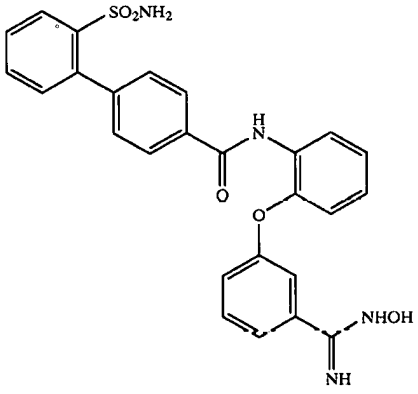
Example 625



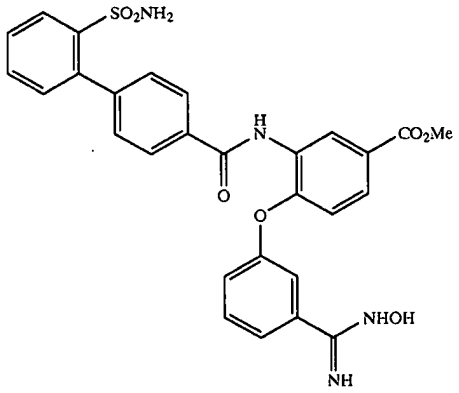
A mixture of compound 20 (1 equiv), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. MS $(M+H)^+$: 487.

Examples 626–631

The following compounds were prepared according to the procedure described in the formation of amidines except that NH_2OH was used instead of NH_4OAc.



MS (M+H):502



MS (M+H):560

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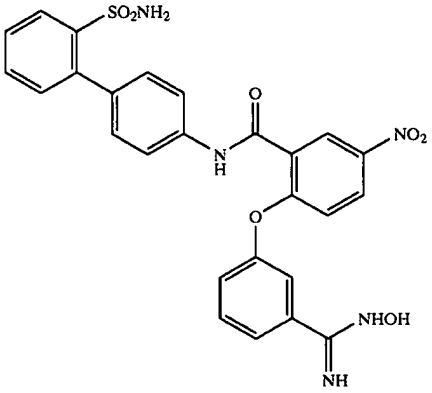
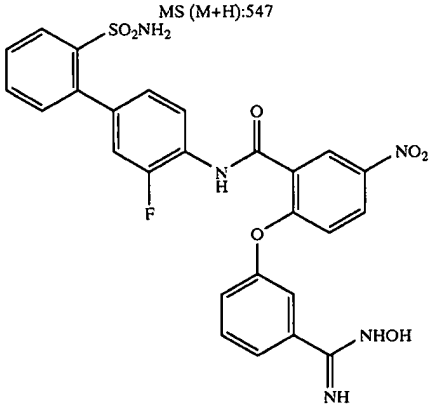
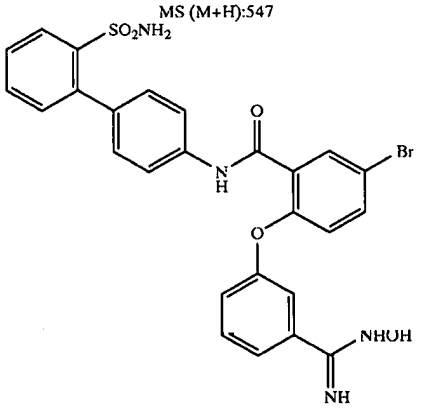


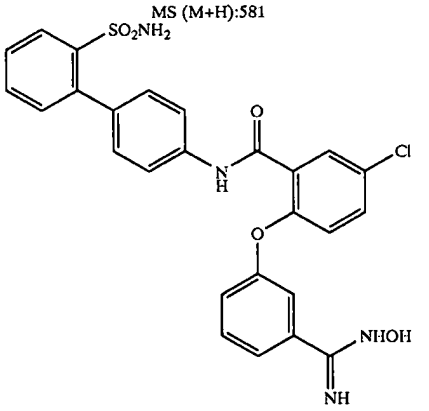
MS (M+H):547



MS (M+H):547



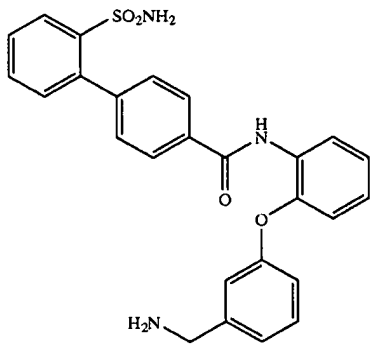
MS (M+H):581



MS (M+H):537

Example 632

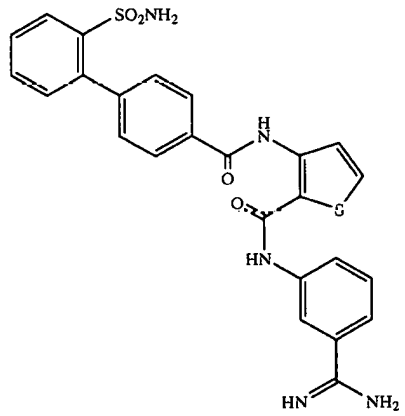
3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzylamine.



A mixture of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl] benzoylamino)phenoxy) benzonitrile (25 mg), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was dried on vacuum pump and then refluxed with 1 mL of TFA for 2 h, evaporated and purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. MS $(M+H)^+$: 500.

Example 633

3-[(3-{[4-(2-sulfamoylphenyl)phenyl] carbonylamino}-2-thienyl)carbonylamino] benzenecarboxamidine



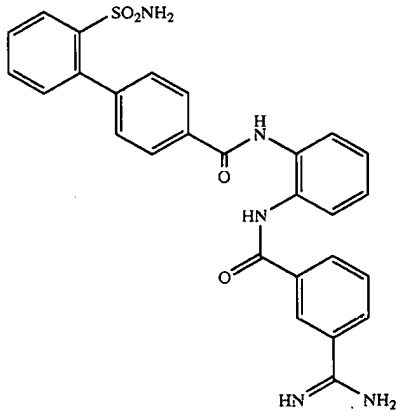
Step 1: A mixture of 3-amino-2-((3-cyanophenyl) aminocarbonyl)thiophene (1 equiv), 4-[(2-t-butylamino-sulfonyl)phenyl]benzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

Step 2: A stream of HCl(g) was bubbled through a 0° C. solution of the compound obtained in step 1 in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was

treated with ammonium acetate (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was evaporated and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. ES-MS 520 (M+1).

Example 634

3-[(3-{[4-(2-sulfamoylphenyl)phenyl] carbonylamino}-2-thienyl)carbonylamino] benzenecarboxamidine



Step 1: A mixture of 2-nitroaniline, 3-cyanobenzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

Step 2: A mixture of the compound obtained in step 1 (1 equiv) and $SnCl_2.2H_2O$ (3 equiv) in 15 mL of EtOAc was refluxed for 2 h. The mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and evaporated.

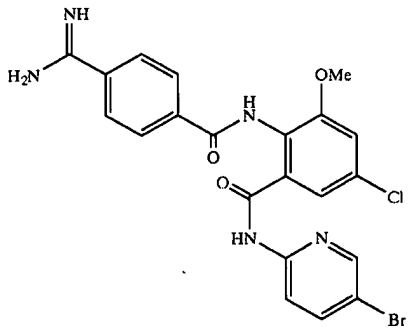
Step 3: A mixture of the compound obtained in step 2 (1 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (1 equiv), pyridine (5 equiv) in 15 mL of dichloromethane was stirred at rt overnight. The mixture was diluted with methylene chloride, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated.

Step 4: A stream of HCl(g) was bubbled through a 0° C. solution of the compound obtained in step 1 in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (5 equiv) in 10 mL of methanol at reflux temperature for 2 h. The solvent was evaporated and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give the title compound. ES-MS 494 (M+1).

Example 635–640

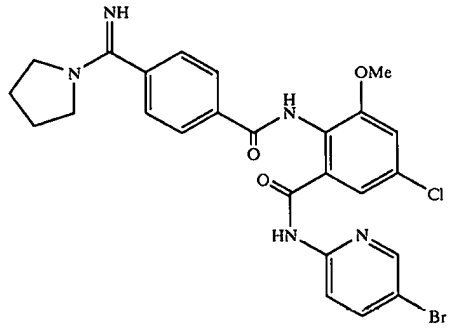
The following compounds were prepared according to the procedure previously described.

Example 635



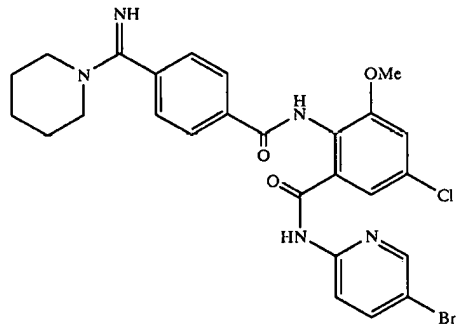
MS (M+H):502

Example 636



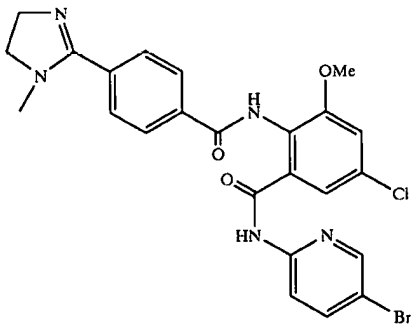
MS (M+H):556

Example 637



MS (M+H):570

Example 638



MS (M+H):542

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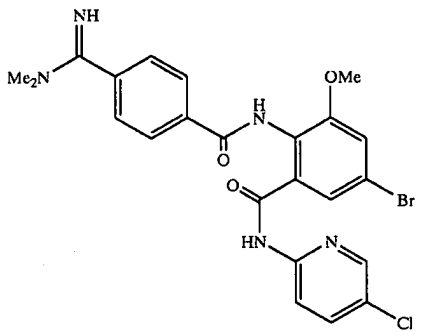
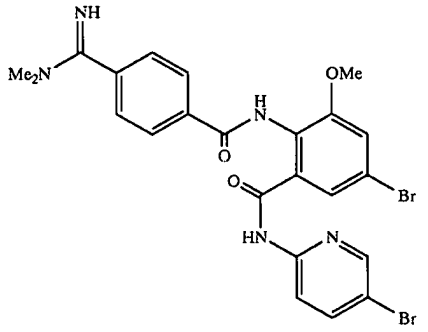
Example 639



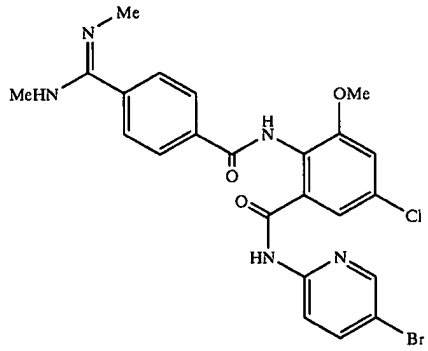
MS (M+H):530

Example 640



MS (M+H):574

Example 641



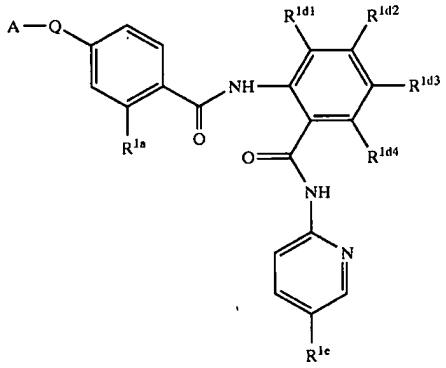
This compound was obtained as a side product in the preparation of Example 322, described earlier, above. ES-MS 530 (M+H).

The above description and illustrative examples show numerous compounds within the formula A-Q-D-E-G-J-X which are potent factor Xa inhibitors. The description and illustrative examples also show the variety of combinations and substituents for each group A, Q, D, E, G, J and X which may be prepared according to the invention and be useful as factor Xa inhibitors. While, for example, compounds having the same A-Q structure but a variety of substituents or D-E-G and/or J-X structures and their substituents are described and shown, the description and illustrative examples are intended to show that compounds of the invention having a different A-Q structure can also have various combinations of D-E-G and/or J-X structures, even though such compounds may not be illustrated in the examples. In other words, each group within the A-Q-D-E-G-J-X, as each is defined above with their substituents, may be varied and combined to form sub-genuses and compounds of the invention. The description and illustrative examples show such combinations and are not intended to limit the sub-genuses or compounds within the A-Q-D-E-G-J-X genus of the invention.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention. All the patents, journal articles and other documents discussed or cited above are herein incorporated by reference.

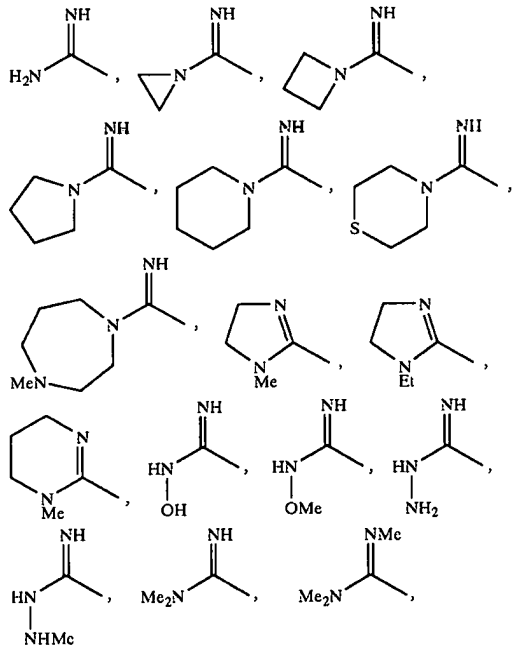
What is claimed:

1. A compound having the formula:



wherein:

A-Q is a member selected from the group consisting of:



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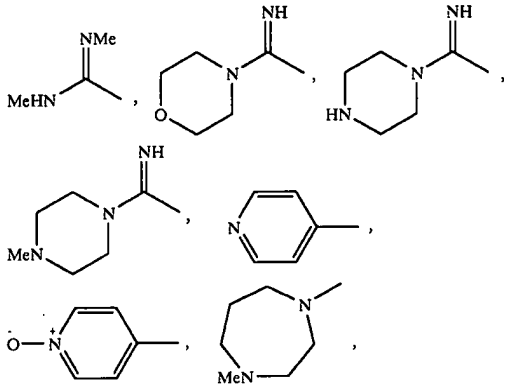
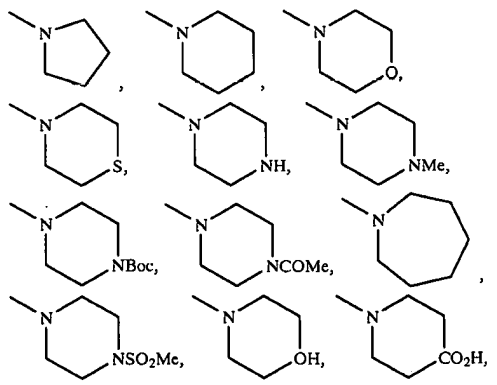


R^{1a} is a member selected from the group of H, F, Cl and Br;

R^{1e} is a member selected from the group consisting of —H, —F, —Cl, —Br, —OMe, —OH, —Me, —CF_3 and —CH_2NH_2;

R^{1d1}, R^{1d2} and R^{1d4} are each H; R^{1d3} is selected from the group consisting of:

H, —Me, —F, —Cl, —Br, aryl, heteroaryl, NH_2, —NMe_2, —NHMe, —$NHSO_2NMe$, —NHCOMe, —CF_3, —OH, —OCH_3, —SCH_3, —OCF_3, —OCH_2F, —$OCHF_2$, —OCH_2CF_3, —OCF_2CF_3, —NO_2, —CN, —CO_2H, —CO_2Me, —CO_2Et, —$CONH_2$, —CONHMe, —$CONMe_2$, —SO_2NH_2, —SO_2CH_3, —SO_2NMe_2, —CH_2OH, —CH_2NH_2, —CH_2NHMe, —CH_2NMe_2, —OCH_2CO_2H, —OCH_2CO_2Me, —OCH_2CO_2Et, —OCH_2CONH_2, —OCH_2CONMe_2, —$OCH_2CONHMe$, —OCH_2CH_2OMe, —OCH_2CH_2OEt, —$OCH_2CH_2NH_2$, —OCH_2CH_2NHMe, —$OCH_2CH_2NMe_2$, —$NHCH_2CH_2OMe$, —SCH_2CH_2OMe, —$SO_2CH_2CH_2OMe$, —$OCH_2CH_2SO_2Me$, —$NHCH_2CH_2NHMe$, —$NHCH_2CH_2NMe_2$, —$N(CH_2CH_2OH)_2$, —$N(CH_2CH_2OMe)_2$, —$NHCH_2CO_2H$, —$NHCH_2CO_2Et$, —$NHCH_2CO_2Et$, —$NHCH_2CONH_2$, —$NHCH_2CONMe_2$, —$NHCH_2CONHMe$, —$N(CH_3)CH_2CO_2H$, —$N(CH_3)CH_2CO_2Et$, —(NMe)CH_2COOH, —N(Me)CH_2CONH_2, —N(Me)CH_2CH_2NMe2, —N(Me)CH_2CH_2OMe, —$NHCH_2CH_2OMe$,



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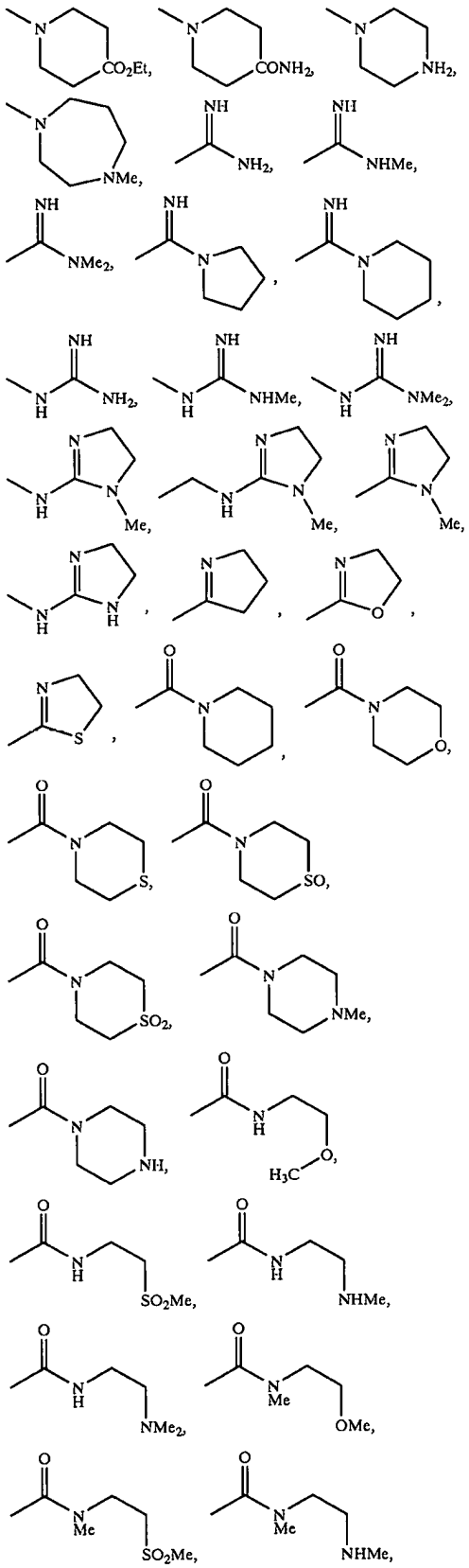

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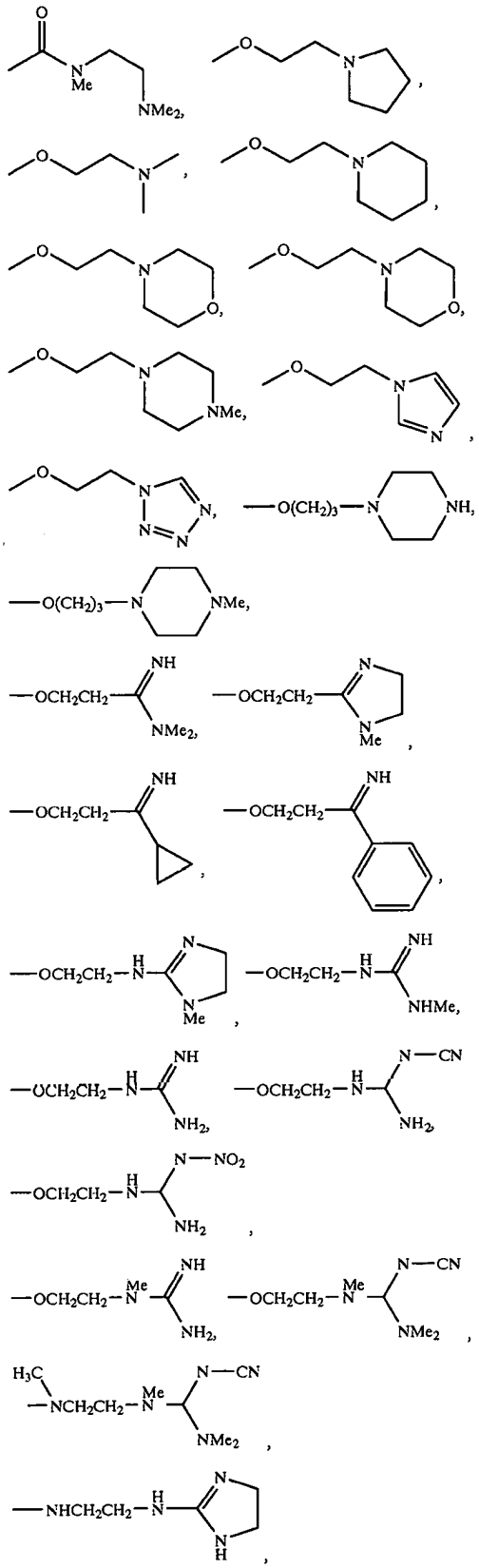

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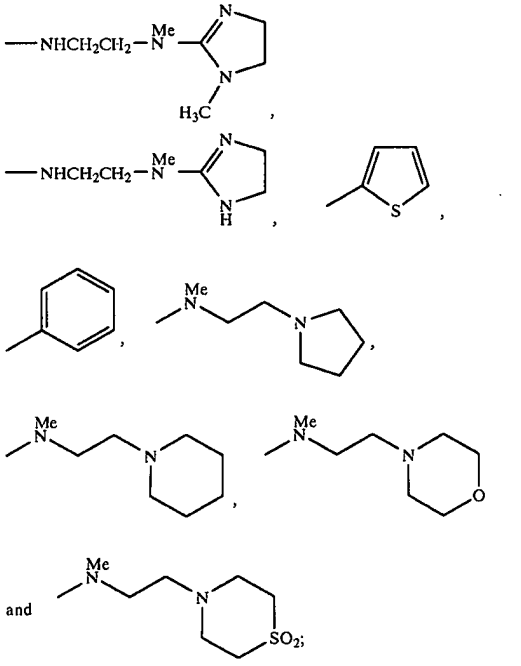
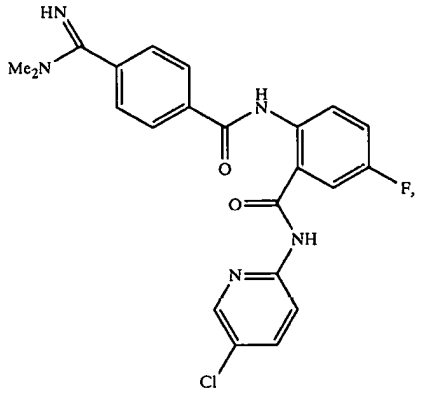
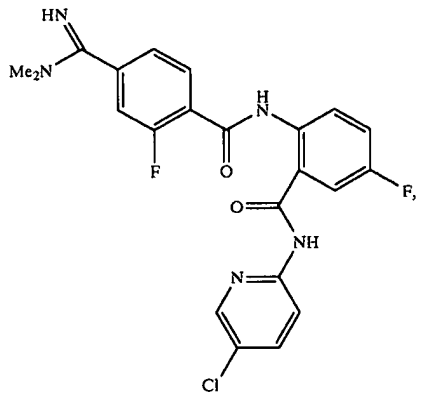


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

2. A compound of claim 1 structure selected from the group consisting of:





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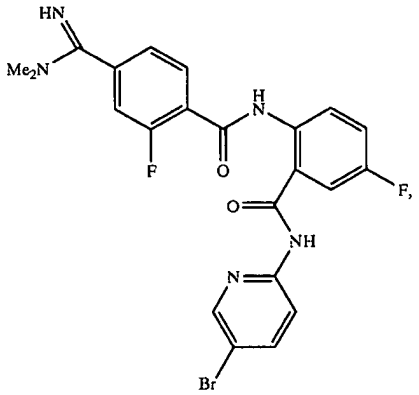

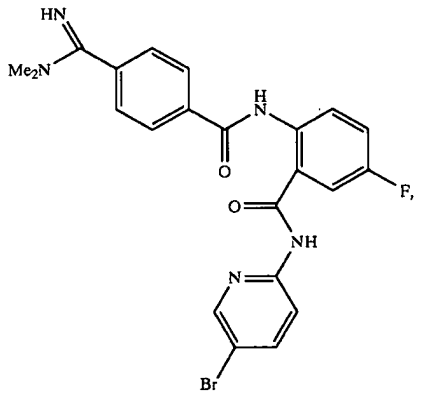

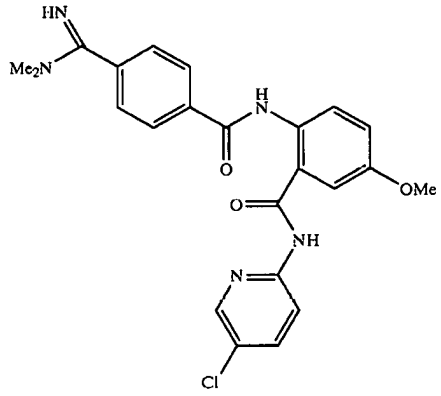

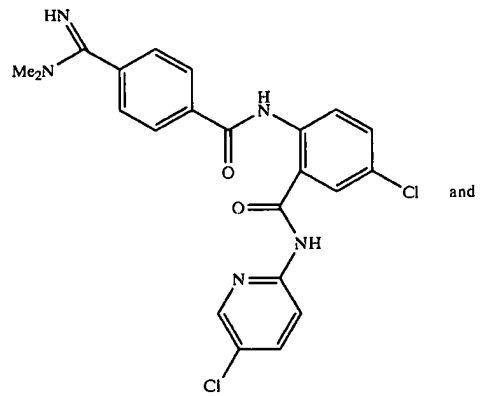

and

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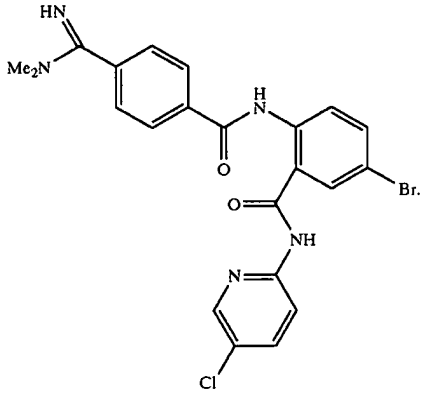
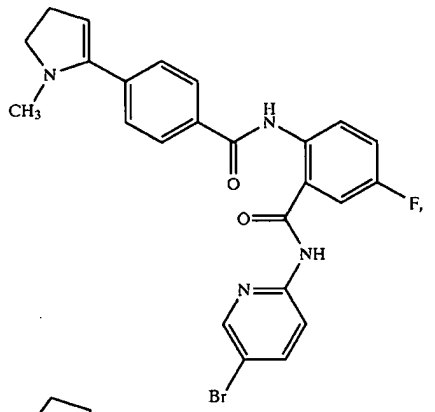
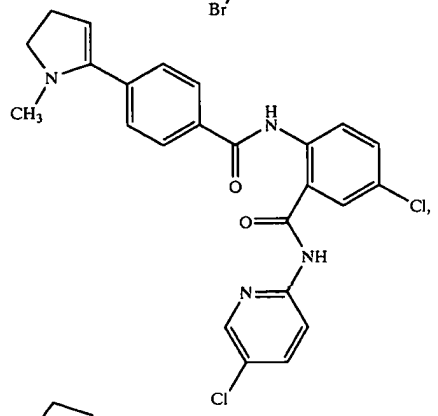
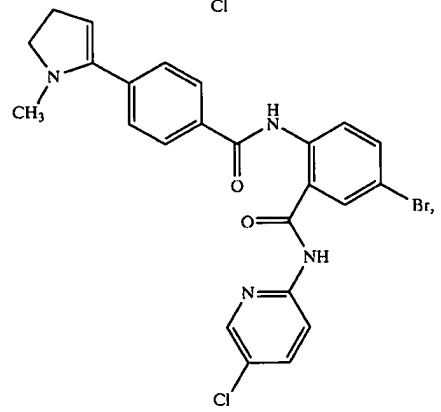


3. A compound of claim **1** having a structure selected from the group consisting of:







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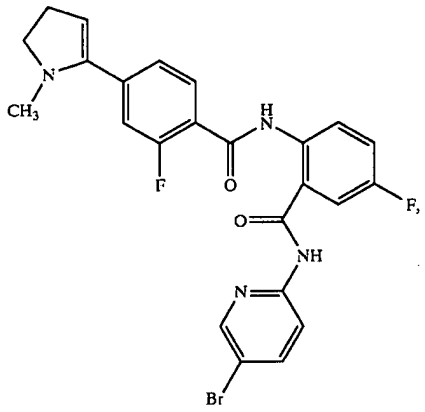

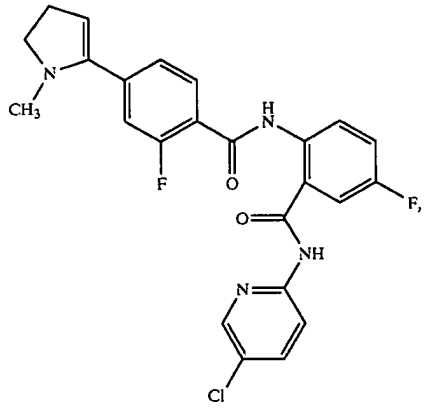

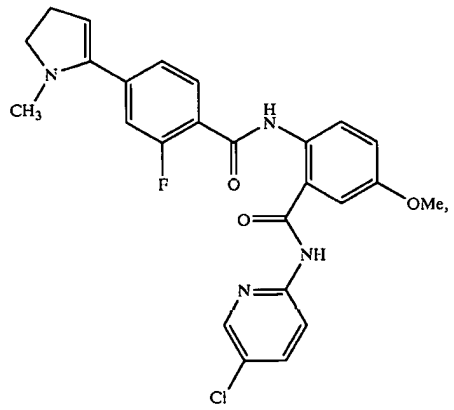

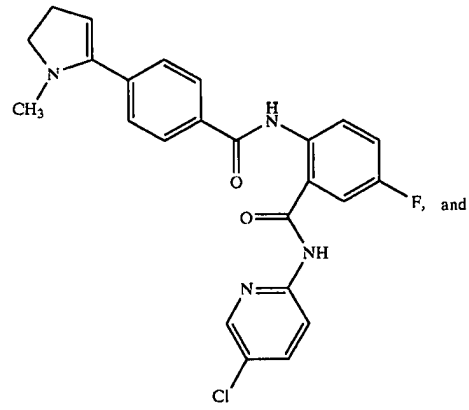

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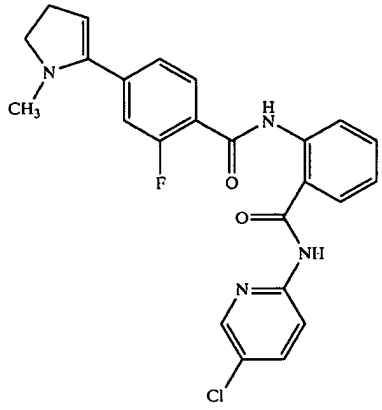
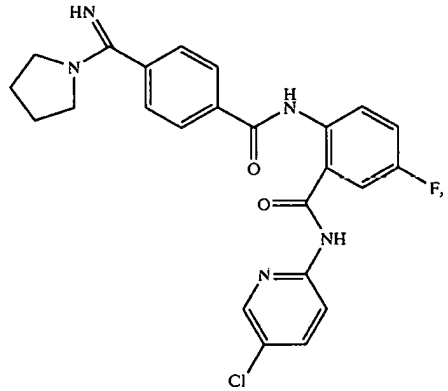
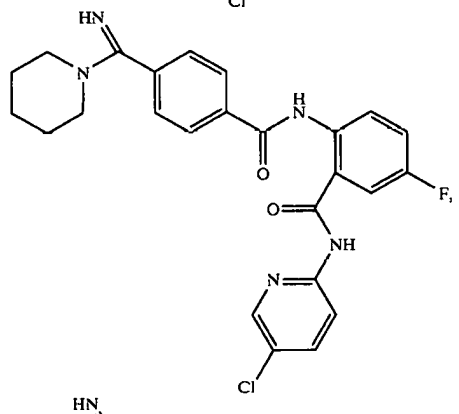
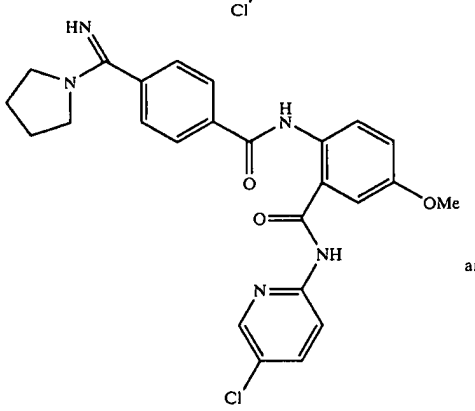


4. A compound claim 1 having a structure selected from the group consisting of:

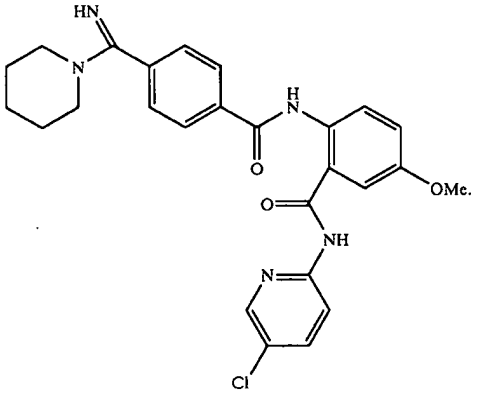




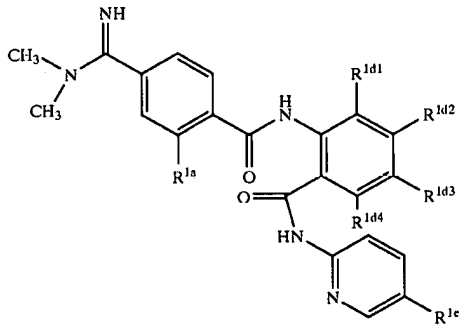


and

-continued



5. A compound of claim 1 having the formula:



wherein:

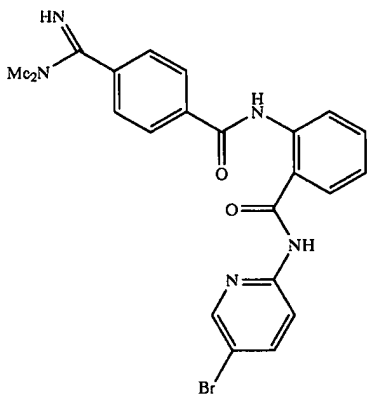
R^{1a} is a member selected from the group of H, F, Cl and Br;

R^{1d1}, R^{1d2}, R^{1d3} and R^{1d4} are each H;

R^{1e} is a member selected from the group of F, Cl, Br, OH, Me and OMe;

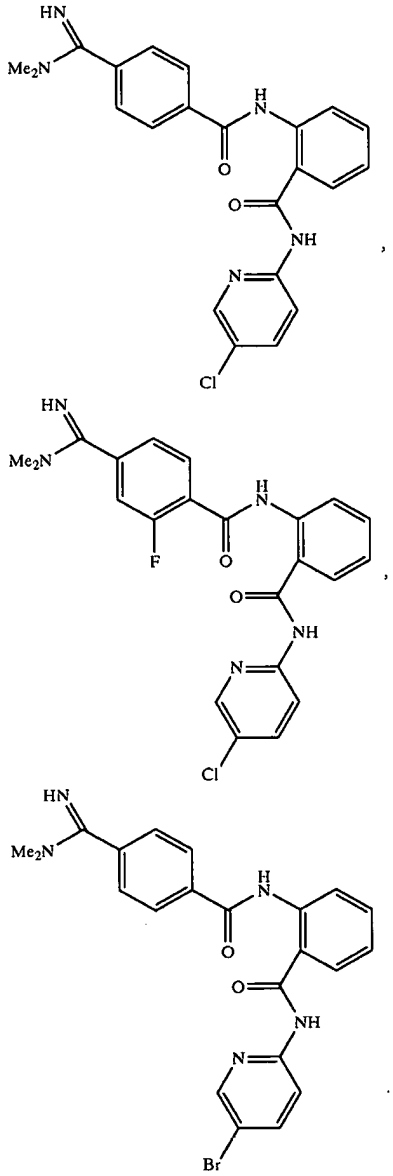
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

6. A compound of claim 5 having a structure selected from the group consisting of:



;

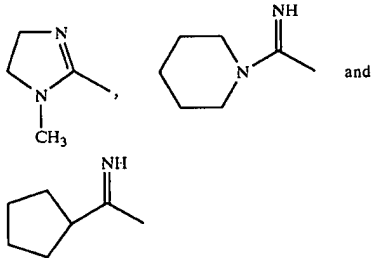
-continued



7. A compound of claim 1:

wherein:

A-Q is a member selected from the group of:



and

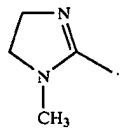
R^{1a} is a member selected from the group of H, F, Cl and Br;

R^{1d1}, R^{1d2}, R^{1d3}, and R^{1d4} are each H;

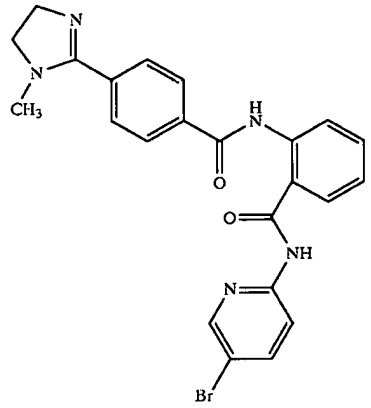
R^{1e} is a member selected from the group of F, Cl, Br, OH, Me and OMe;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

8. A compound of claim **7**, wherein A-Q is:



9. A compound of claim **8** having a structure selected from the group consisting of:



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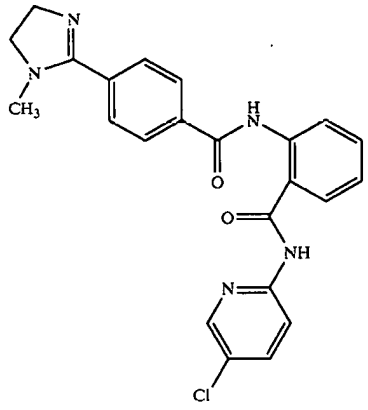

, and

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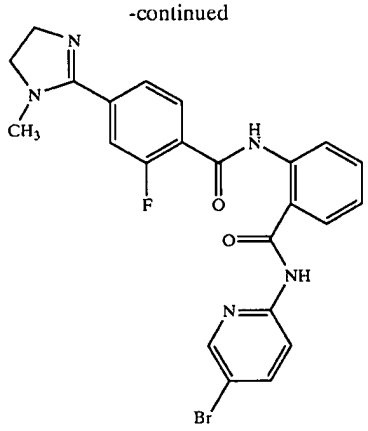
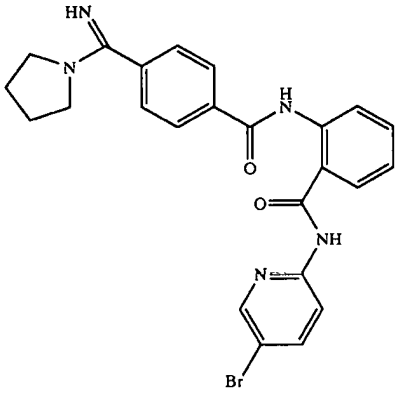


10. A compound of claim **7** having a structure selected from the group consisting of:



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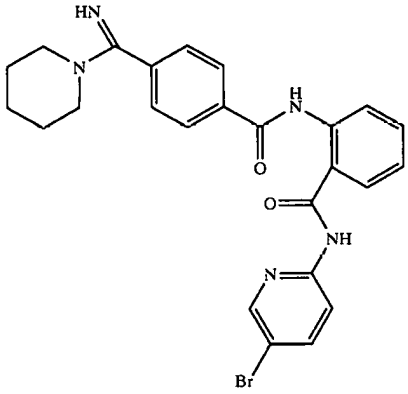

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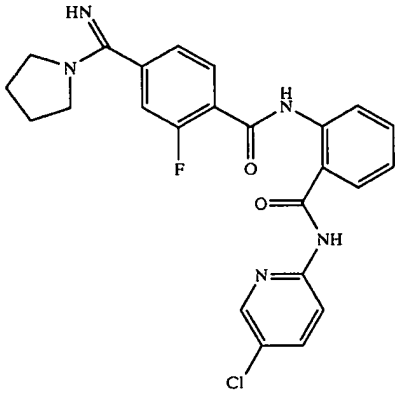

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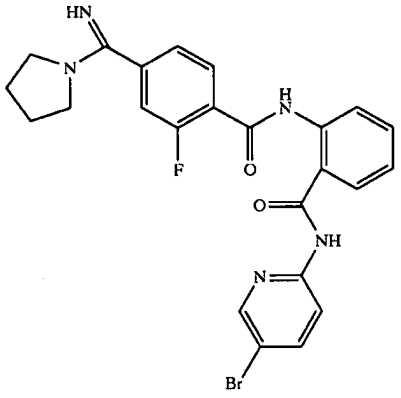
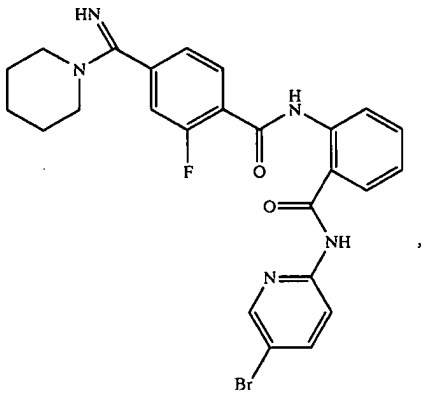
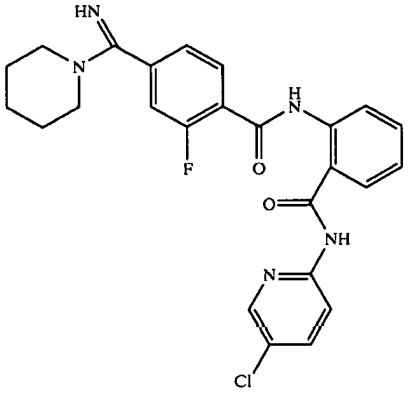
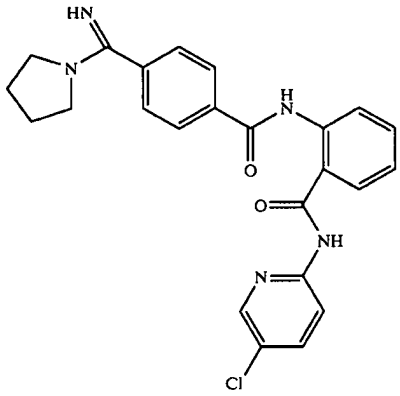




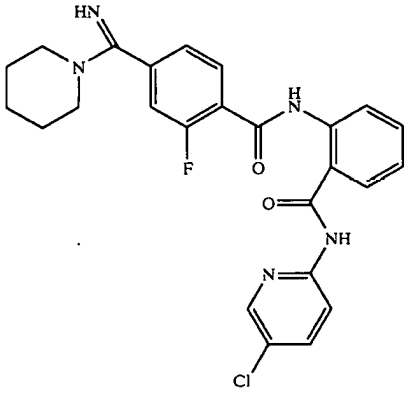


and

-continued



and



11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of claim 1.

* * * * *

Exhibit E

United States Patent and Trademark Office

Office of the Commissioner for Patents

BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
6835739	10687334	10/15/2003	12/28/2004

Payment Window Status

No maintenance fees are due.

WINDOW	STATUS	FEES
11.5 Year	Closed	Paid

Window	First Day to Pay	Surcharge Starts	Last Day to Pay	Status	Fees
3.5 Year	12/28/2007	07/01/2008	12/29/2008	Closed	Paid
7.5 Year	12/28/2011	06/29/2012	12/28/2012	Closed	Paid
11.5 Year	12/28/2015	06/29/2016	12/28/2016	Closed	Paid

Patent Holder Information

Customer # 25188

Entity Status UNDISCOUNTED

Phone Number 3123806500

Address

Dennemeyer & Co., LLC
181 West Madison Street
Suite 4500
Chicago, IL 60602
UNITED STATES

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

CURRENT MAINTENANCE FEE ADDRESS
DENNEMEYER & CO., LLC
181 WEST MADISON STREET
SUITE 4500
CHICAGO, US 60602

CUSTOMER #
25188

ENTITY STATUS
UNDISCOUNTED

STATEMENT GENERATED
08/16/2017 13:00:36

Invention

BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
6835739	10687334	10/15/2003	12/28/2004

Payment Details

PAYMENT DATE	DATE POSTED	TRANSACTION ID	ATTORNEY DOCKET #	TOTAL PAYMENT
06/19/2008	06/19/2008	061908INTMTFEE00008319132159		$930.00

Fee Code	Description	Safe ID	Fee Amount
1551	MAINTENANCE FEE DUE AT 3.5 YEARS	061908INTMTFEE00008319	$930.00

According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

CURRENT MAINTENANCE FEE ADDRESS	CUSTOMER #	ENTITY STATUS	STATEMENT GENERATED
DENNEMEYER & CO., LLC 181 WEST MADISON STREET SUITE 4500 CHICAGO, US 60602	25188	UNDISCOUNTED	08/16/2017 13:01:24

Invention

BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
6835739	10687334	10/15/2003	12/28/2004

Payment Details

PAYMENT DATE	DATE POSTED	TRANSACTION ID	ATTORNEY DOCKET #	TOTAL PAYMENT
05/30/2012	05/31/2012	053112RAMBULKS00011690504623		$2,850.00

Fee Code	Description	Sale ID	Fee Amount
1552	MAINTENANCE FEE DUE AT 7.5 YEARS	053112RAMBULKS00011690	$2,850.00

According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution the payment will be void and the maintenance fee and any necessary surcharge unpaid.

United States Patent and Trademark Office

Office of the Commissioner for Patents

Maintenance Fee Statement

CURRENT MAINTENANCE FEE ADDRESS
DENNEMEYER & CO., LLC
181 WEST MADISON STREET
SUITE 4500
CHICAGO, US 60602

CUSTOMER #
25188

ENTITY STATUS
UNDISCOUNTED

STATEMENT GENERATED
08/16/2017 13:02:06

Invention

BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

PATENT #	APPLICATION #	FILING DATE	ISSUE DATE
6835739	10687334	10/15/2003	12/28/2004

Payment Details

PAYMENT DATE	DATE POSTED	TRANSACTION ID	ATTORNEY DOCKET #	TOTAL PAYMENT
06/20/2016	06/20/2016	062016INTMTFEE12102700		$7,400.00

Fee Code	Description	Sale ID	Fee Amount
1553	MAINTENANCE FEE DUE AT 11.5 YEARS	062016INTMTFEE00010446	$7,400.00

According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Exhibit F

PTO/SB/26 (08-03)

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT	Docket Number (Optional) 021390-0040410US

In re Application of: Bing-Yan Zhu et al.

Application No. 10/687,334

Filed: October 15, 2003

For: BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa

The owner, Millennium Pharmaceuticals, Inc. of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. 6,376,515 B2. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☒ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☐ The undersigned is an attorney of record.

Ian Robert Silverman 5/26/04

Signature Date

Ian Robert Silverman

Typed or printed name

☒ Terminal disclaimer fee under 37 CFR 1.20(d) is included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

*Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP § 324.

60218274 v1

Exhibit G

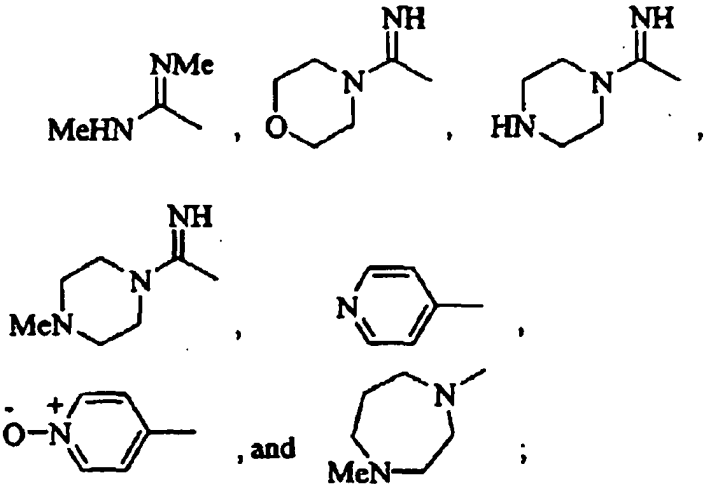
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,835,739 B2
APPLICATION NO. : 10/687334
DATED : December 28, 2004
INVENTOR(S) : Zhu et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 451 (claim 1 continued), at approximately line 15, please correct the chemical drawing to read:



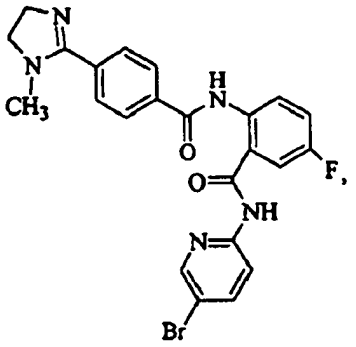
UNITED STATES PATENT AND TRADEMARK OFFICE

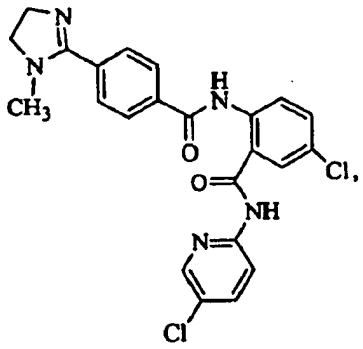
CERTIFICATE OF CORRECTION

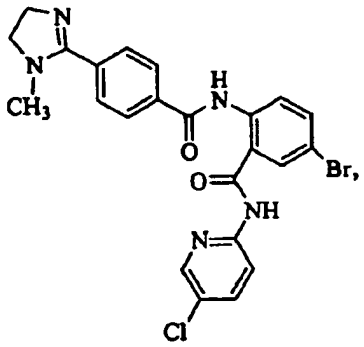
PATENT NO. : 6,835,739 B2
APPLICATION NO. : 10/687334
DATED : December 28, 2004
INVENTOR(S) : Zhu et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 456 (claim 3), at approximately line 20, please correct the chemical drawing to read:







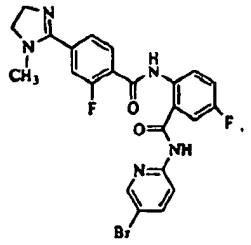
UNITED STATES PATENT AND TRADEMARK OFFICE

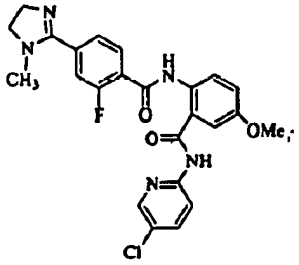
CERTIFICATE OF CORRECTION

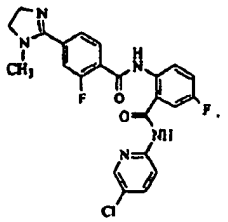
PATENT NO. : 6,835,739 B2
APPLICATION NO. : 10/687334
DATED : December 28, 2004
INVENTOR(S) : Zhu et al.

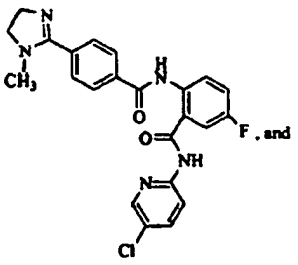
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 457 (claim 3 continued), at approximately line 1, please correct the chemical drawing to read:









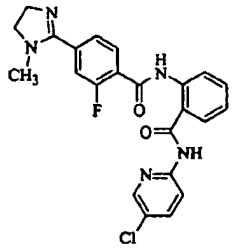
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

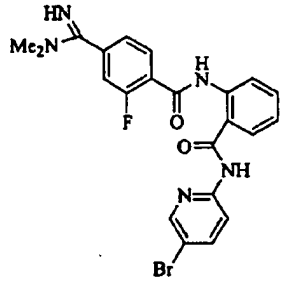
PATENT NO. : 6,835,739 B2
APPLICATION NO. : 10/687334
DATED : December 28, 2004
INVENTOR(S) : Zhu et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

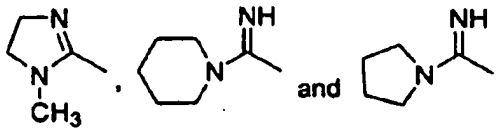
In column 458 (claim 3 continued), at approximately line 1, please correct the chemical drawing to read:



In column 460 (claim 6 continued), at line approximately 37, please correct the chemical drawing to read:



In column 460 (claim 7), at approximately line 64, please correct the chemical drawing to read:



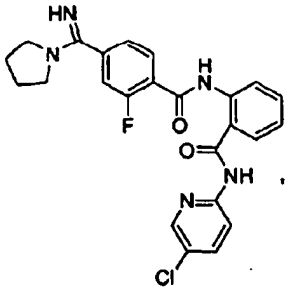
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

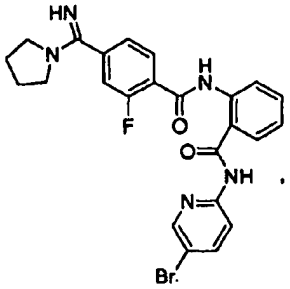
PATENT NO. : 6,835,739 B2
APPLICATION NO. : 10/687334
DATED : December 28, 2004
INVENTOR(S) : Zhu et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

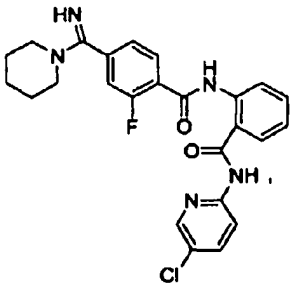
In column 462 (claim 10), at approximately line 60, please correct the chemical drawing to read:



In column 463 (claim 10 continued), at approximately line 12, please correct the chemical drawing to read:



In column 463 (claim10 continued), at approximately line 43, please correct the chemical drawing to read:



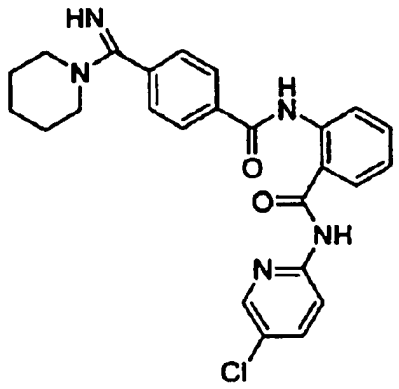
UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,835,739 B2
APPLICATION NO. : 10/687334
DATED : December 28, 2004
INVENTOR(S) : Zhu et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 464 (claim 10 continued), at approximately line 31, please correct the chemical drawing to read:



Signed and Sealed this

Twenty-sixth Day of September, 2006

JON W. DUDAS
Director of the United States Patent and Trademark Office

Exhibit H

Betrixaban Maleate
IND 072,679
FDA Chronological Correspondence Log

No	Date To/From FDA	Serial #	Description
1	01-25-05	N/A	Email requesting preferred IND format
2	05-06-05	N/A	Tox information request in anticipation of Pre-IND Meeting
3	5-9-05	N/A	Unsigned copy of Pre-IND Type C Meeting Request (Questions regarding preclinical program) sent in advance of submission per Reviewer request.
4	5-24-05	N/A	Response to 5-9-05 Meeting Request (meeting denied with written responses to Points for Concurrence provided in 5-9-05 meeting request).
5	8-3-05	N/A	Pre- IND Type C Meeting Request (cQT prolongation issues/data review)
6	8-19-05	N/A	Letter granting 8-3-05 meeting request
7	8-25-05	N/A	Transmittal of Pre-IND Meeting Briefing Document
8	9-09-05	N/A	ROC requesting that Pre-IND meeting scheduled for December 6th be rescheduled. Pre-IND meeting rescheduled to 12/14/05
9	9-13-05	N/A	Addendum to 8-3-05 Meeting request – requesting participation by specific FDA representatives (meeting granted via teleconference scheduled for 11-10-05)
10	10-10-05	**0000**	Submission of Original New Drug Application
11	10-20-05	N/A	Confirmation of receipt of IND
12	11-29-05	N/A	FDA Minutes of 11-10-05 teleconference
13	11-30-05	N/A	Comments and Recommendations from clinical review of the Original New Drug Application dated10-10-05
14	12-2-05	**0001**	Response to FDA request for information from 11-10-05 teleconference
15	12-2-05	N/A	Response to questions posed in the 8-25-05 Briefing Document received via email.
16	12-6-05	N/A	Email regarding 12/14/05 Pre-IND meeting attendees
17	12-7-05	N/A	Diane Leaman, FDA, sends list of attendees for 12/14/05 meeting in response to 12/6/05 email
18	12-15-05	N/A	Transmittal of "back-up" slides used during FDA Pre-IND meeting of December 14, 2005
19	12/16/05	N/A	Email to Diane Leaman requesting meeting with tox reviewer.
20	1-4-06	N/A	FDA minutes of December 14, 2005 meeting
21	1-25-06	N/A	Email to Diane Leaman, FDA, follow-up on agreements reached at 12-14-05 FDA meeting
22	1-26-06	N/A	Email from Diane Leaman, FDA, follow-up on agreements reached at 12-14-05 FDA meeting
23	2-1-06	**0002**	Response to FDA minutes of December 14, 2005

Betrixaban Maleate
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FDA Chronological Correspondence Log

No	Date To/From FDA	Serial #	Description
24	3-8-06	0003	Protocol Amendment – New Protocol for Study **05-003** (EXPERT); sample informed consent and transfer of obligations
25	3-8-06	0004	Information Amendment – Toxicology/Pharmacology: : 3 non-clinical studies and analysis of metabolite levels in the MAD study as requested by FDA at the December 14, 2005 Pre- IND Type C meeting.
26	4-10-06	N/A	Email record of contact – follow-up on status of review Serials 0003 and 0004. Review not complete.
27	5/10-5/11-06	N/A	FDA informed Portola that the Medical Officer did not have any questions on the EXPERT protocol submitted in IND protocol amendment, Serial No. 3 but that there will be a letter forthcoming with review comments on the pharmacology review of pharm/tox IND amendment #4. FDA noted that the EXPERT study could proceed.
28	6-2-06	N/A	FDA comments from review of IND Amendment, SN0004.
29	6-15-06	0005	Protocol Amendment - Investigator Documentation – Study **05-003** (EXPERT)-Bowen, Fox, Gill Jove, Muntz, Swank
30	7-05-06	0006	Protocol Amendment – New Protocol Study #06-004
31	7-05-06	0007	Information Amendment – CMC. Information for 3 SR tablet formulations at 5, 10 and 15% HPMC. Update of API batch analysis table and stability data. Update of IR capsule batch analysis and stability data.
32	7-27-06	0008	Protocol Amendment - Investigator Documentation – Study #05-003 (EXPERT) Kruse, Stiff, Vasicek
33	8-03-06	0009	IND Safety Report – Initial Report (IND Safety Report #1 for EXPERT Study – Protocol **05-003**)
34	8-29-06	0010	Protocol Amendment – Investigator Documentation – Study #05-003 (EXPERT) Hoe, Mant, Profitt
35	10-12-06	0011	Protocol Amendment – Investigator Documentation – Study #05-003 (EXPERT) ABUZGAYA, FISHER, PUSKAS, DESSOUKI
36	11-03-06	0012	Information Amendment: Pharmacology/Toxicology, request for input from Tox. reviewer on doses proposed for a 9-month toxicology study in the dog
37	12-08-06	N/A	Response to SN0012 requesting an additional dose of 50 mg/kg/day in addition to the doses proposed (0, 3, 10, and 30 mg/kg/day)
38	11-03-06	0013	Protocol Amendment – Investigator Documentation – Study #05-003 (EXPERT) BLUM, TURNBULL, GUERRA, updated 1572 for Dr. David Fox adding an additional study site.
39	1-18-07	0014	Protocol Amendment – New Investigator Documentation, updated 1572 for Dr. Jove-additional laboratory.
40	1-18-07	0015	Annual Report and updated IB, and change in regulatory contact

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No	Date To/From FDA	Serial #	Description
41	2/1/07	0016	Request for telecon regarding letter received on 12/8/06 – FDA request for addition of a top dose of 50 mg.
42	2/6/07	N/A	Email to Diane Leaman letting her know that that the request for a telecon was sent to the Division last week.
43	2/16/07	N/A	FDA cancelled meeting and agreed to proceed with doses originally proposed by Portola of (0, 10, and 30 mg/kg/day)
44	2/22/07	0017	Information Amendment: Pharmacology/Toxicology, Results and full draft report from recent tissue distribution and mass balance with dosimetry - ^{14}C toxicology study conducted in Rats and 2 additional draft toxicology reports: 90-Day Dog, 90-Day Rat.
45	3/1/07	N/A	Informal email asking Project manager for insight into cause for recommendation change to the original doses proposed by Portola for 9-month tox study in dogs.
46	3/4/07	N/A	Telephone contact report: Diane Leaman left a voicemail message stating that the Division had no further comments.
47	3/14/07	0018	Protocol Amendment – New Protocol with investigator information (Dr. Leese) Protocol 07-008
48	4/3/07	0019	Protocol Amendment – New Protocol **07-009**, with draft ICF and Transfer of Obligations – (IRB approval and Investigator Documentation Pending)
49	4/12/07	0020	Updated 1572 for PI and Investigational study site location
50	4/25/07	N/A	Email request for information – Agency preference for receipt of Phase 1 CSRs – Abbreviated or Full.
51	4/25/07	N/A	Email request for information – Confirm receipt of all Serial Numbers through 0020.
52	4/26/07	N/A	Project Manager confirmed that all SNs through 0020 had been received.
53	4/26/07	0021	Type B Meeting Request – End of Phase II Conference (Briefing Document to Follow)
54	5/2/07	0022	Investigator information as follow-up to SN0019
55	5/2/07	N/A	Project Manager stated that full Clinical Study Reports should be submitted, but that the back-up copies could be submitted on CD-ROM
56	5/02/07	N/A	Response to 4/26/07 EOPII Type B Meeting request meeting granted and scheduled on June 27, 2007. *(no electronic file, no paperwork in log)*
57	5/9/07	0023	Final Clinical Study Reports (**05-002** and **04-001**). Draft of 04-001 submitted in the original IND.

Betrixaban Maleate
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FDA Chronological Correspondence Log

No	Date To/From FDA	Serial #	Description
58	5/15/07	N/A	Discussion, via email, with Diane Leaman regarding lack of attendance by Dr. Temple at the June 27, 2007 End-of-Phase II meeting.
59	5/25/07	0024	Briefing Document for granted EOPII Meeting scheduled for 6-27-07
60	6/15/07	0025	Response to FDA Request for Information – Clinical Pharmacology Table for QTc Interdisciplinary Review Team
61	6/15/07	0026	30-day Notice of Intent to submit Non-Clinical Carcinogenicity Proposed Protocol
62	7-19-07	N/A	Meeting minutes from above noted End-of-Phase II meeting held with FDA on June27, 2007.
63	8-1-07	0027	Follow-up to SN0026 submission Seeking Point for Concurrence regarding to need to conduct an animal carcinogenicity study for the initial indication (anti-platelet therapy in prevention of DVT in the setting of total knee- or hip-replacement surgery.
64	8-20-07	0028	Protocol Amendment - New Protocol **#07-011**, entitled "A Phase I Study to Compare the Pharmacokinetic Properties of Different Formulations of PRT054021 in Healthy Subjects"
65	8-21-07	0029	Information Amendment - CMC describing the chemistry, mfg. and controls of both Immediate- and Delayed-release (enteric-coated) tablets
66	9/12/07	0030	Change in Sponsor's Authorized Representative to Janice Castillo
67	9/18/07	0031	Protocol Amendment - New Protocol 07-013, entitled: A Double-Blind Randomized Single Dose Crossover Trial to define the ECG effects of Betrixaban (formerly PRT054021 and MLN1021) using a Clinical and a Supratherapeutic Dose compared to Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough ECG Trial and Response to FDA Request for Information noted in the 7-19-07 End-of-Phase II meeting minutes. Updated IB
68	9/19/07	0032	Protocol Amendment – New Protocol **#06-005** "An open-label, single-dose, mass-balance study to assess the disposition of 14c-labeled PRT054021 in healthy male subjects"
69	9/21/07	0033	Correction to SN0031 amendment above: not a double-blind study
70	9/26/07	Email	Email to Diane Leaman RE: update on review of SN0027, Carci proposal
71	10/1/07	0034	CMC amendment to above (SN0032) Protocol #06-005 "An open-label, single-dose, mass-balance study to assess the disposition of 14c-labeled PRT054021 in healthy male subjects"
72	10/15/07	Letter	Re: amendment 027, granting waiver for carci study for indications of thromboembolism & knee/hip replacement, but still requiring carci data to support chronic indications.
73	10/18/07	Email	Re: request for update on QTC submission review

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No	Date To/From FDA	Serial #	Description
74	10/31/07	0035	Information amendment: Preliminary Absolute Bioavailability data. For QTC review
75	11/06/07	0036	Updated 1572 for Protocol **07-011**
76	11/06/07	N/A	Clinical comments on amendment SN0031.
77	11/09/07	Letter	Re: #031 QTC protocol, FDA go ahead for QTc study, along with request for additional information
78	11/20/07	0037	Protocol Amendment – Investigator Documentation - Protocol #07-013 – Thorough QT Study
79	12/5/07	0038	Protocol Amendment: Protocol # **07-013** increasing # of subjects to 96
80	12/17/07	0039	Investigator Documentation – Updated 1572 Protocol # 07-013
81	1/16/08	0040	IND Annual Report
82	1/28/08	0055	Correction to IND # on Annual Report cover page, and FDA requested **adjustment to Serial Numbering now starting with SN0055.**
83	4/9/08	Ref only	See Betrixaban AF IND log for filing of original IND for AF indication
84	5/6/08	Email	Email String from/To responding to questions back and forth about the logistics of submitting final QT data, pertaining to both this IND and 102,130.
85	5/7/08	0056	Filing final CSRs (filed reports only in hardcopy, all appendices on CDROM): **07-012** (absolute bioavailability in healthy volunteers-CTA, EUDRACT 207-004047-30), AND **06-004**: PK of 3 SRs vs IR oral 40mg in healthy volunteers (see SN0006)
86	5/27/08	0057	EXPERT **05-003** final clinical study report (CSR)
87	7/7/08	0058	Final CSR of **06-005** Mass Balance study and an Overview of Metabolite information
88	7/14/08	0059	Draft audited Tox Reports NC-07-0085 6 month rat, and NC-07-0095 9 month dog
89	7/21/08	0060	Final CSR # **07-008**."The effects of a proton pump inhibitor, or an antacid, on the pharmacokinetic properties of a solid formulation of PRT054021 (betrixaban) administered to healthy subjects as a single oral dose"
90	8/4/08	0061	Final CSR **#07-013** "Thorough QT study" and submission of new protocol for AFib – #08-015 (DRAFT) (entirety of CSR was filed on CD ROM only)
91	08/04/08	N/A	Janice Castillo informs Diane Leaman that the TQT report has been submitted via CD-ROM (xfiled IND 102,130)

Betrixaban Maleate
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FDA Chronological Correspondence Log

No	Date To/From FDA	Serial #	Description
	08/21-22/08	N/A	Diane Leaman requests QTcI & its alpha datasets. Datasets downloaded by Devi Kozeli, FDA for Michael Li's (FDA QTc Data Manager) review via Mike Thorn's (Statistical Resources) server (8-22-08). (xfiled IND 102,130)
92	08/22/08	ROC	Telephone Record of Contact: Telecon between Portola, FDA, and Statistical Resources (Mike Thorn). FDA proposed another dataset duplicating existing raw data and including additional information requests by Michael Li. (xfiled IND 102,130)
93	08/25/08	N/A	Follow-up email from Statistical Resources, verifying FDA's receipt of additional TQT data analysis set. (xfiled IND 102,130)
94	8/25/08	**0062**	Additional Information for TQT Study. Dataset adding QTcI and its alpha to the raw dataset. Submitted as CD-ROM.
95	08/29/08	N/A	Follow-up emails between Portola and FDA regarding TQT data analysis set. (xfiled IND 102,130)
96	09/26/08	0063	Information Amendment—CMC Amendment; Hovione/Patheon (CTD paper & electronic format)
97	10/28/08	N/A	Inquiry to Diane Leaman regarding status of Committee review of Thorough QT study. Committee review was completed with no comments.
98	11/14/08	0064 Sec 1-15 Sec 16	Amended Final Study Report, Protocol **07-013** for TQT Study
99	12/16/08	0065	Information Amendment: Clinical Study Reports for Study **06-005** (amended) and Study **07-009**
100	01/12/09	0066	IND Annual Report In Progress. CD-Rom includes filing and appended study reports: NC-06-0072, NC-06-0073, NC-07-0096, NC-08-0220, NC-08-0166
101	01/29/09	0067	Updated Metabolite Information Amendment
102	04/02/09	0068	IND Safety Report: Initial Written Report, Study **08-015**; 100020-001 (full report to 102,130, SN0027)
103	04/09/09	0069	Information Amendment: CMC
104	04/27/09	0070	IND Safety Report: Follow-up Report, Study **08-015**; 100020-001 (full report to 102,130, SN0029)
105	05/21/09	0071	IND Safety Report: Initial Written Report, Study **08-015**; 200013-002/A-T (full report to 102,130, SN0031)
106	06/15/09	0072	Investigator's Brochure (dated April 1, 2009)
107	06/15/09	0073	30 Day Notice: Request for Carcinogenicity Special Protocol Assessment (SPA)

Betrixaban Maleate
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FDA Chronological Correspondence Log

No	Date To/From FDA	Serial #	Description
108	07/08/09	FROM	FDA Response to SN0067.
109	07/20/09	0074	SPA Request: 104 Week Rat Carci Study Protocol; final report NC-07-0085 *Note:* Letter only and CD-ROM for NC-07-0085 submitted only as cross-ref
110	08/11/09	FRO M/TO	Marcus Cato, FDA, emails Janice Castillo to inform that the 5/21/09 submission 0031 (typo in email--s/b 0071) requires full safety report as opposed to cover letter only to 72,679. Janice responds that the full reports are going to IND 102,130 and addressed to the Division of Cardiovascular and Renal Drug Products as responsible division. Cover letter only to 72,679 (Div. of Med Imaging and Hematology) to avoid double reporting.
111	08/19/09	FRO M	Marcus Cato responds that full SAEs may be sent to 72,679 as correspondences to avoid double reporting.
112	08/19/09	0075	IND Safety Report: Follow-up Written Report, Study **08-015**; (full report to 102,130, SN0039
113	08/26/09	ROC	Janice Castillo and Marcus Cato confirm that SAEs sent as correspondences to IND 72,679 would commence beginning with SAE reported in his 8/11/09 email (SN0071)
114	08/28/09	0076	Protocol Amendment: New Protocol **09-018** (food study).
115	09/08/09	0077	General Correspondence – providing SAEs to 72,679 (formerly only sent as cover pages for reference only)
116	09/14/09	0078	Final Report, Study 07-011; Pharmacokinetic Study
117	11/05/09	0079	IND Safety Report: Initial Written Report, Study **08-015**
118	11/12/09	0080	IND Safety Report: Initial Written & Follow Up Reports, Study **08-015**
119	12/18/09	0081	Protocol Amendment: New Protocol 001-00 (PN001) and New Investigator Gutierrez
120	01/07/10	0082	Annual Progress Report (Nonclinical Reports via CD-ROM)
121	01/07/10	0083	CMC Amendment: Addition of Merck as API manufacturer
122	01/25/10	0084	Protocol amendment: Amendment to 001-00 (SN 0052 in 102,130))
123	06/2/10	0085	CSR: Study **08-014** Digoxin
124	07/06/10	N/A	FDA Responds to Protocol 001-00, Food Effects Study (SN0081) with Clinical Pharmacology questions.
125	08/03/10	0086	DEC Protocol (**006-00**), IB, New Investigator Marquez, TORO
126	08/05/10	0087	CMC Amendment for Merck as Manufacturer and API Form II; New DP Label Strength.
127	08/27/10	0088	Type C Meeting Request
128	08/31/10	0089	Protocol Amendment: New Protocol 010-00 (Verapamil)
129	09/01/10	0090	Protocol Amendment: New Protocol 011-00 (Biocomparability)

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IND 072,679
FDA Chronological Correspondence Log

No	Date To/From FDA	Serial #	Description
130	09/02/10	N/A	Alison Blaus emails Janice Castillo to request an electronic copy of the meeting request (SN0056)
131	09/02/10	N/A	Janice Castillo emails Alison Blaus the electronic copy of the meeting request.
132	09/07/10	N/A	Janice Castillo and Alison Blaus discuss dates for the Type C Meeting.
133	09/07/10	N/A	Alison Blaus emails Type C Meeting Confirmation for November 16, 2010 meeting.
134	09/09/10	N/A	Janice Castillo confirms Nov 9 meeting date.
135	09/21/10	0092	Response to FDA letter (Protocol 01-00)
136	09/21/10	0093	Protocol Amendment: Protocol 06-00 Amendment 1 (DEC)
137	09/22/10	0091	Merck: Protocol Amendment: New Investigators, **PN006**
138	09/30/10	0094	Protocol Amendment: New Protocol PN003 (Japan); CMC: Updated placebo sections
139	10/07/10	N/A	Janice Castillo emails Alison Blaus to ask her preference on the Type C Briefing doc—what she would like hardcopy, what she would like on CD
140	10/07/10	0095	Type C Briefing Document
141	10/08/10	N/A	Alison Blaus responds to Janice Castillo's 10/07/10 email that CD for the full CSR is acceptable in each copy. Janice responds she will also send an email of the full submission.
142	11/03/10	0096	Merck: Protocol Amendment: New Investigators, **PN006**
143	11/07/10	N/A	Alison Blaus emails Janice Castillo preliminary responses for Type C Meeting
144	12/07/10	N/A	Alison Blaus emails the Type C Meeting Minutes
145	01/04/11	0097	Annual Progress Report for period 01 October 2009 to 30 September, 2010 (CD Contents)
146	01/07/11	0098	Merck: Protocol Amendment: New Investigator, **PN006**
147	01/07/11	0099	Merck: Information Amendment-Clinical (Updated Investigator Information, **PN006)**
148	01/21/11	0100	Merck: IND Safety Report: **PN006**; Initial; 0060042; anemia, GI bleed
149	01/24/11	0101	Letter requesting FDA feedback on Phase 3 proposal for a Non-inferiority trial using dabigatran as the comparator.
150	02/01/11	0102	Merck: IND Safety Reports: **PN006**; Follow-up- 0060042; GI Hemorrhage; Initial-0060012; Thrombocytopenia
151	02/01/11	0103	EOP2 Meeting Request
152	02/08/11	0104	Merck: IND Safety Report, **PN006**: Follow-up 2; 0060042; GI Hemorrhage
153	02/10/11	N/A	Alison Blaus emails Janice Castillo the EoP2 meeting confirmation

Betrixaban Maleate
IND 072,679
FDA Chronological Correspondence Log

No	Date To/From FDA	Serial #	Description
154	02/16/11	0105	Merck: IND Safety Report, **PN006**; Follow-up 3; 0060042; GI Hemorrhage; follow-up 2-0060012; Thrombocytopenia
155	02/16-2/17/11	N/A	Janice follows up SN0069 request for feedback. Alison Blaus says that the reviewers are scheduled for an internal meeting next week.
156	02/21/11	0106	Merck: IND Safety Report, **PN006**; Follow-up 4; 0060042; GI Hemorrhage
157	02/25/11	N/A	Taranum Singh, FDA, informs Janice Castillo that Cardiology, Allergy and Neurosciences will lead on EOP2 meeting, on May 9, 2011.
158	02/25/11	N/A	Alison Blaus emails summary of FDA discussion regarding Phase 3 advice.
159	02/28/11	0107	Merck: Protocol Amendment: New Investigator, **PN006**
160	02/28/11	0108	Merck: Protocol Amendment: New Investigator, **PN006**
161	02/28/11	N/A	Alison Blaus emails Janice Castillo the Phase 3 Advice Letter
162	03/03/11	N/A	Janice Responds to Taranum Singh that Portola accepts the meeting date.
163	03/07/11	0109	Merck: IND Safety Report, **PN006**; Follow-up 5; 0060042; GI Hemorrhage
164	03/09/11	0110	Merck: IND Safety Report, **PN006**; Initial; 0060025; Rectal Hemorrhage
165	03/11/11	N/A	FDA Advice Letter to no longer send duplicate submissions. All submissions to 102,130.
166	03/15/11	0111	Merck: IND Safety Report, **PN006**; Follow-Up; 0060025; Rectal Hemorrhage
167	03/18/11	N/A	ROC: Jance speaks to Tyree Newman, FDA, regarding 03/11/11 Advice Letter. Exception submissions to 72,679 will be SAEs, CMC amendments and the IND Annual Report.
168	04/07/11	0112	Merck: IND Safety Report, **PN006**; Follow-up 6; 0060042; GI Hemorrhage
169	04/14/11	0113	Merck: IND Safety Report, **PN006**; Follow-up 7; 0060042; GI Hemorrhage
170	04/27/11	0114	Merck: IND Safety Report, **PN006**; Follow-up 8; 0060042; GI Hemorrhage
171	05/02/11	0115	Request for advice Ph3 – Questions re: Medically ill pts (CD ROM-References)
172	05/06/11	N/A	Janice Castillo and Tyree Newman discuss Protocol submission
173	05/17/11	N/A	Janice Castillo emails Tyree Newman to ask whether they should schedule a telecom now regarding the Protocol submission and if the Agency requires additional information or if their review is as scheduled.

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No	Date To/From FDA	Serial #	Description
174	05/19/11	N/A	Tyree Newman informs Janice Castillo that questions will be addressed by July 10, 2011.
175	05/20/11	N/A	Janice Castillo emails Tyree Newman and asks if FDA agrees with EU ultrasound policy. EU CHMP guidance attached.
176	06/13/11	N/A	Tyree Newman emails Janice Castillo a copy of the response to 05/02/11 Questions. (US Mail Original attached in paper).
177	07/15/11	N/A	Janice Castillo emails Tyree Newman to request date for EoP2 meeting
178	07/19/11	N/A	Tyree Newman suggests Portola send a written formal EoP2 meeting request.
179	08/12/11	0116	EOP2 Meeting Request and draft questions.
180	08/12/11	N/A	Janice Castillo emails Tyree Newman a copy of SN0116.
181	08/18/11	N/A	Tyree Newman informs Janice Castillo that Portola will be granted a one-hour face-to-face meeting. Times TBD.
182	08/29/11	N/A	Tyree Newman sends the Meeting Granted Letter and instructions on submitting the EoP2 Briefing.
183	09/19/11	N/A	Janice Castillo confirms that 9/26/11 is final submission date of EOP2 Briefing document.
184	09/26/11	0117	End of Phase 2 Briefing document
185	09/27-28/11	N/A	Janice emails the betrixaban IB to Tyree Newman
186	10/03/11	N/A	Corrected CD ROM of SN0117.
187	10/04/11	N/A	Janice Castillo emails Tyree Newman the highlights of the clinical pharmacology table
188	10/05/11	0118	Supplemental docs to the EOP2 briefing: Investigator's Brochure and Clinical Pharmacology table as emailed to Tyree Newman on 09/28 and 10/04.
189	10/16-17/11	N/A	Janice Castillo inquires about the status of the preliminary review of the EOP2 Briefing document (SN0117)
190	10/20/11	N/A	Tyree Newman emails preliminary responses to EOP2 Briefing
191	10/23/11	N/A	Stuart Heminway emails Tyree Newman Portola's response to FDA's EOP2 comments
192	10/24/11	0119	Reply to FDA preliminary responses
193	10/25/11	N/A	Janice emails Tyree to inform that Portola will be sending Portola's meeting summary of Question 4 for inclusion in FDA's minutes of the EOP2 meeting
194	10/31/11	N/A	Tyree informs Janice that the Question 4 summary cannot be included in the minutes, but sends a response to Question 4.
195	11/01/11	0120	Request of Teleconference to discuss remaining questions from EOP2 meeting

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196	11/01/11	N/A	Janice Castillo emails Tyree Newman a copy of SN0120.
197	11/04/11	N/A	FDA denies request for follow-up meeting
198	11/07/11	N/A	FDA Minutes of EOP2 Meeting
199	11/10/11	N/A	FDA letter denying follow-up meeting in lieu of written response
200	11/22/11	0121	Request for CMC advice
201	11/30/11	N/A	Janice Castillo emails Tyree Newman to request FDA Minutes of the **EOP2** meeting
202	12/01/11	N/A	Tyree Newman responds that EOP2 minutes are being finalized
203	12/02/11	N/A	Responses to questions not addressed at EOP2 meeting
204	01/06/12	0122	Submission providing evidence for use of 20 mg enoxaparin in patients with severe renal dysfunction in the Phase 3 study and our proposal for documentation of immobility
205	01/09/12	0123	IND Annual Progress Report
206	01/23-24/12	N/A	Todd Lorenz emails Ann Farrell to ask to reconsider enoxaparin comparison studies. Dr Farrell advices Portola send formal meeting request.
207	01/26-27/12	N/A	Janice Castillo and Tyree Newman confirm that the Agency is willing to move forward with the meeting request.
208	01/30/12	0124	Request for Meeting to Resolve 10-day Ultrasound Issue
209	02/03/12	N/A	Meeting Request Granted letter for 2/10/12 Type A meeting.
210	02/07/12	0125	Type A Meeting Materials – presentation slides
211	02/07/12	N/A	Janice Castillo emails Tyree Newman a copy of the Type A meeting Materials
212	02/08/12	N/A	Tyree responds to 02/07, reminding to factor in time for minutes and discussion.
213	02/09/12	N/A	Janice Castillo asks Tyree Newman if it is possible to change procedure for taking minutes; confirmation of Drs. Temple and Pazdur; additional attendees; request FDA slides.
214	02/17/12	N/A	FDA Minutes from 2/10/12 Type A Meeting
215	02/21/12	N/A	Janice Castillo requests response for SN0122
216	02/22/12	0126	Phase 3 Protocol **11-019**; Transfer of Regulatory Obligations
217	02/24/12	N/A	Janice Castillo emails Tyree Newman a copy of SN0126.
218	03/16/12	0127	CMC Amendment
219	03/19/12	N/A	Janice Castillo summarizes 0127
220	03/28/12	N/A	Tyree Newman acknowledges 0127
221	03/28/12	N/A	Tyree Newman emails FDA's CMC advice
222	04/04/12	0128	Response to FDA Meeting Minutes of 10 Feb 2012

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223	04/12/12	0129	11-019 New Investigator Submission by PPD
224	04/24/12	0130	11-019 Protocol Amendment 1
225	04/25-26/12	ROC	Email excerpts confirming that FA CDRP does not want SUSARS from 72,679 submitted to 102,130
226	05/04/12	N/A	FDA Advice on reporting SAEs
227	05/15/12	0131	11-019 New Investigator Submission by PPD
228	06/15/12	0132	11-019 New Investigator Submission by PPD
229	07/13/12	0133	11- 019 New Investigator Submission by PPD
230	07/18/12	NA	FDA sends CMC advice from questions asked in the EOP2 letter (SN0121)
231	08/10/12	N/A	Notice of FDA hold of Clexane shipment (received 08/22/12)
232	08/15/12	0134	11- 019 New Investigator Submission by PPD
233	09/17/12	0135	11- 019 New Investigator Submission by PPD
234	10/17/12	0136	11- 019 New Investigator Submission by PPD
235	10/22/12	N/A	Notice of FDA Action
236	11/16/12	0137	11- 019 New Investigator Submission by PPD
237	12/17/12	0138	11- 019 New Investigator Submission by PPD
238	01/08/13	NA	Janice Castillo requests confirmation from Tyree Newman that submitting the DSUR on CD-ROM is acceptable
239	01/09/13	NA	Tyree Newman responds that CD-ROM is acceptable
240	01/10/13	0139	DSUR: Reporting Period: 01 October 2011 to 30 September 2012 (International version)
241	01/11/13	NA	Janice Castillo informs Tyree Newman that due to technical problems, the DSUR is submitted via hardcopy
242	01/16/13	0140	Request for Feedback: APEX IDMC and eCRFs
243	01/17/13	0141	11- 019 New Investigator Submission by PPD
244	02/15/13	0142	11- 019 New Investigator Submission by PPD
245	02/15/13	0143	Change in Protocol: 11-019 Protocol Amendment 2
246	02/26-27/13	NA	FDA emails advice letter regarding SN0140, APEX IDMC
247	03/18/13	0144	11- 019 New Investigator Submission by PPD

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248	04/29/13	0145	11- 019 New Investigator Submission by PPD
249	05/21/13	0146	11- 019 New Investigator Submission by PPD
250	06/25/13	0147	11- 019 New Investigator Submission by PPD
251	07/31/13	0148	11- 019 New Investigator Submission by PPD
252	08/30/13	0149	11- 019 New Investigator Submission by PPD
253	9/18/13	0150	Drug Product Amendment; TORO
254	10/07/13	0151	11- 019 New Investigator Submission by PPD
255	11/08/13	0152	Request for Type C Meeting
256	11/20/13	N/A	Type C Meeting Granted: January 21, 2014, 1pm
257	11/19/13	0153	11- 019 New Investigator Submission by PPD
258	12/13/13	0154	CMC Amendment
259	12/18/13	N/A	FDA Request for electronic courtesy copy of Type C Briefing
	12/19/13	N/A	Manish Anand sends courtesy copy of Type C Briefing document: Briefing (Word)
260	12/19/13	0155	Type C Briefing Document
261	12/20/13	0156	11- 019 New Investigator Submission by PPD
262	12/23/13	N/A	Discussion of delivery of desk copies and Dr. Temple's attendance to the Type C Meeting
263	12/23/13	N/A	Foreign Visitor Request forms for Drs Hull and Cohen.
264	01/09/14	N/A	Preliminary FDA responses to meeting questions.
265	01/14/14	N/A	Dial-in Type C Preparation Telecon information
266	01/28/14	N/A	Type C Meeting follow-up with meeting slides.
267	02/04/14	0157	11- 019 New Investigator Submission by PPD
268	02/06/14	N/A	FDA Meeting Minutes from Type C Meeting

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269	02/11/14	0158	Development Safety Update Report 002
270	03/11/14	0159	11- 019 New Investigator Submission by PPD *(NTF: Typographical error on volume separator, page 454. Should be SN0159 03/11/14* ***not*** *SN0157 02/04/14).*
271	03/18/14	0160	IND Safety Report: Initial Written Report
272	04/14/14	0161	Request for advice on Protocol 11-019 Amendment 3
273	04/16/14	N/A	Manish Anand emails copy of 0161.
274	04/29/14	0162	11- 019 New Investigator Submission by PPD
275	05/14/14	N/A	FDA requests clarification for 0161.
276	05/16/14	N/A	FDA emails clinical comments re: request for advice (0161)
277	05/22/14	N/A	Manish Anand sends email after call for clarification to FDA's clinical questions of 05/22/14
278	05/23/14	N/A	FDA informs PTLA that it is discussing its response to FDA request
279	05/30/14	N/A	FDA emails clarification on comments (05/14/14) regarding 0161.
280	06/13/14	0163	Protocol Amendment 3
281	06/16/14	N/A	Manish Anand sends courtesy email confirming delivery of 0163.
282	06/27/14	0164	11- 019 New Investigator Submission by PPD
283	07/31/14	0165a	Request for Fast Track Designation
284	08/01/14	0165b	Correction to the 1571 for SN0165
285	08/06/14	N/A	Receipt of Request for Fast Track Designation (rec'd 08/14/14)
286	08/14/14	0166	11- 019 New Investigator Submission by PPD
287	09/22/14	N/A	Manish Anand emails Janet Higgins a link to the draft in AHJ manuscript regarding the 11-019 Amendment, "RECOGNITION OF BIOMARKER IDENTIFIED HIGH RISK PATIENTS IN THE APEX STUDY RESULTING IN A PROTOCOL AMENDMENT".

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288	10/01/14	N/A	Fast Track Designation Request denial.
289	10/07/14	0167	11- 019 New Investigator Submission by PPD
290	11/11/14	0168	Type C Meeting Request
291	11/14/14	0169	11- 019 New Investigator Submission by PPD
	11/19/14	N/A	FDA sends via USPS information for Type C Meeting briefing package shipment
292	11/25/14	N/A	Meeting request granted (0168) as telecom on 1/26/15.
293	12/01/14	ROC	Portola requests appeal of 01/26/15 telecom as a face-to-face meeting. FDA responds no appeal process, proceed with telecom and request face-to-face if telecom outcome is not satisfactory.
294	12/19/14	0170	DSUR 003
295	12/23/14	0171	Type C Briefing Package
296	01/05/15	N/A	Manish Anand requests confirmation of Type C Briefing Package and desk copies
297	01/09/15	N/A	Janet Higgins confirms receipt of Type C Package and desk copies.
298	01/23/15	N/A	FDA Response to Type C Meeting
	01/24/15	N/A	APEX Formal Meeting
299	01/30/15	0172	11- 019 New Investigator Submission by PPD
300	03/20/15	N/A	Request for NDA number
301	03/24/15	N/A	Manish Anand emails FDA question regarding the use of an 80 mg single-unit dosage form to compare systemic exposure profiles to confirm bioequivalence
302	03/25/15	0173	11- 019 New Investigator Submission by PPD
303	03/26/15	N/A	FDA confirms and agrees with use of 80 mg single unit dosage
304	03/26/15	0174	Request for Comment and Advice on an IND
305	03/27/15	0175	Type C Meeting Request

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306	04/10/15	N/A	Type C Meeting Request Granted. Scheduled for June 25, 2015
307	05/01/2015	0176	IND Safety Report: Initial Written Report (Mfr. Report No. 2015PRT000071)
308	05/08/2015	0177	11-019 New Investigator Submission by PPD
309	05/13/2015	0178	IND Safety Report: Follow-up #1 to a Written Report
310	05/21/2015	0179	Type C Meeting Briefing Package
311	06/02/2015	N/A	FDA provided like to Providing Regulatory Submission in Electronic Format
312	06/02/2015	0180	IND Safety Report: Follow-up #3 to a Written Report
313	06/11/2015	N/A	Request for Feedback from Agency regarding SAP
314	06/12/2015	N/A	Provided Agency with Foreign Visitor Data Request Form for Type C Meeting (Dr. Russell Hull)
315	06/12/2015	N/A	Response from FDA regarding Feedback from Agency regarding SAP
316	06/12/2015	N/A	Agency Confirms Receipt of - Foreign Visitor Data Request Form for Type C Meeting (Dr. Russell Hull)
317	06/12/2015	N/A	Questions sent to FDA regarding SAP, requesting feedback from the FDA Statistical Reviewers
318	06/12/2015	0181	New Investigator Submission
319	06/17/2015	0182	Request for Type C Meeting and Briefing Materials
320	06/17/2015	0183	Request for Agency Feedback (Comment and Advice on an IND)
321	06/18/2015	N/A	Courtesy Copy of an IND Amendment for a "Request for a Type C Meeting and Briefing Materials submitted to the IND as SN0182
322	06/18/2015	N/A	Courtesy copy of an IND Amendment for a request for "Comment and Advice on an IND submitted to the IND as SN0183
323	06/18/2015	N/A	FDA confirmed receipt of SN0182 "Request for a Type C Meeting and Briefing Materials"

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324	06/18/2015	N/A	FDA confirmed receipt of SN0183 "Request for Comment and Advice on an IND"
325	06/18/2015	N/A	Teleconference number and slide deck prepared for the introduction to the meeting scheduled for 25 June 2015
326	06/19/2015	N/A	FDA's preliminary response to meeting questions.
327	06/19/2015	N/A	Security check for meeting scheduled for 25Jun2015
328	06/19/2015	N/A	FDA preliminary response to meeting questions (25 June 2015)
329	06/23/2015	N/A	Courtesy Copy of Preliminary Comments for your June 25th meeting
330	06/23/2015	N/A	Confirmation that requested teleconference has been granted with statistical review team
331	06/24/2015	N/A	Type C Meeting Request granted for 28 July 2015 (Discussion of the SAP)
	07/07/2015	Letter	Formal Mtg Min Type C Fast Track
332	07/09/2015	0184	Submission: APEX Study (Protocol 11-019) Sample Size Re-Assessment
333	07/09/2015	N/A	E-mail Correspondence: Sample Size Re-Assessment for APEX study (Protocol 11-019)
334	07/10/2015	N/A	E-mail Confirmation Receipt of Correspondence: Sample Size Re-Assessment for APEX study (Protocol 11-019)
335	07/10/2015	N/A	Correspondence: Courtesy Copy of Meeting Minutes for Type C Meeting on June 25, 2015
336	07/13/2015	N/A	Correspondence regarding Telecon: Telephone call-in information for July 28, 2015 Type C Meeting
337	07/13/2015	N/A	Correspondence: Confirming receipt of desk copies and call in numbers. Attached preliminary responses to meeting questions
338	07/13/2015	N/A	Correspondence: Portola Confirms receipt of Agency's preliminary responses to Portola's meeting questions
339	7/16/2015	N/A	Correspondence: Portola requests meeting time extension for Type C Telecon meeting (July 28, 2015)

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340	7/16/2015	N/A	FDA Correspondence – Type C Meeting (June 25, 2015)
341	7/21/2015	N/A	Correspondence: Preliminary responses to meeting questions (Type C Meeting, Guidance)
342	7/21/2015	N/A	Correspondence: Portola follow-up on meeting time extension for Type C Telecon Meeting (July 28, 2015)
343	7/22/2015	N/A	Correspondence: Follow-up email to correspondence
344	7/22/2015	N/A	Correspondence: Portola provided Type C Meeting Summary Documents and Slides for FDA Type C Meeting on Betrixaban: Statistical Analysis Plan (July 28, 2015)
345	7/27/2015	N/A	Correspondence: Portola provided updated slides for Type C Meeting
346	7/27/2015	N/A	Correspondence: FDA confirmed receipt of updated slides for Type C Meeting
347	7/29/2015	N/A	Email Correspondence: Teleconference follow-up regarding SAP
348	8/03/2015	N/A	Email Correspondence: Follow-up in regards the teleconference 7/28/2015 SAP
349	8/06/2015	N/A	Letter of Authorisation for European Regulatory Solutions (ERS) Ltd.
350	08/07/2015	0185	Protocol Amendment: New Protocol 15-020
351	08/07/2015	N/A	Email Correspondence: Request for Information (queries)
352	08/07/2015	N/A	Email Correspondence: Confirmation Receipt of email regarding Queries
353	08/12/2015	0186	Response to FDA Request for Information
354	8/10/2015	N/A	Teleconference – FDA provided Meeting Minutes (Type C) from Meeting 7/28/2015
355	08/12/2015	N/A	Email Correspondence: Response to FDA regarding Queries, with submission Cover Letter attached.
356	8/13/2015	0187	Protocol Amendment: New Investigator 11-019
357	8/19/2015	0188	Request for Fast Track Designation

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358	8/20/2015	N/A	Correspondence – Fast Track Application Courtesy Copy of SN0188 to Janet Higgins
359	8/20/2015	N/A	Correspondence – Fast Track Application Courtesy Copy and inquiry for Meeting Minutes with Diane Hanner
360	8/20/2015	N/A	Acknowledgement receipt from Diane Hanner of Fast Track Designation Courtesy Copy
361	8/20/2015	N/A	Correspondence - Meeting Minutes from Type C Meeting (July 28, 2015)
362	8/25/2015	N/A	Correspondence – confirmation of receipt of copy of Portola's response to comments from Agency
363	8/27/2015	N/A	Correspondence – acknowledgement receipt of Fast Track Designation
364	8/28/2015	N/A	Correspondence – confirmation of no additional comments regarding sample size re-assessment
365	9/03/2015	0189	Information Amendment – Chemistry, Manufacturing and Controls
366	9/08/2015	0190	Safety Report (Follow-Up #4) Protocol 11-019
367	9/11/2015	N/A	Correspondence – submission of BE Study to the FDA
368	9/15/2015	N/A	Correspondence – Acknowledgement receipt of BE Study now being reviewed
369	9/17/2015	0191	Protocol Amendment: New Investigator 11-019
370	9/22/2015	0192	Safety Report (Initial) Protocol 11-019
371	9/28/2015	N/A	Correspondence – FDA granted Fast Track Review
372	9/30/2015	0193	Information Amendment: Statistics (SAP)
373	10/1/2015	0194	Safety Report (Initial) Protocol 11-019
	10/2/2015	Letter	Courtesy copy of Grant Fast Track
374	10/7/2015	0195	Protocol Amendment: New Investigator BE Study
375	10/7/2015	N/A	Correspondence – courtesy copy of Grant Fast Track

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376	10/7/2015	N/A	Correspondence - comments on Protocol Amendment 15-020 Betrixaban Capsules
377	10/15/2015	0196	Safety Report (Follow-up #1) Protocol 11-019
378	10/20/2015	0197	Request for Proprietary Name Review
379	10/28/2015	0198	Protocol Amendment: New Investigator 11-019
380	11/2/2015	0199	Safety Report (Initial) Protocol 11-019
381	11/3/2015	0200	Study No. 15-020 – Response to FDA Comments
382	11/12/2015	N/A	E-mail Correspondence regarding Comments to SAP
383	11/16/2015	N/A	E-mail Correspondence regarding SAP, requesting Telecon
384	11/19/2015	N/A	e-mail correspondence responding to FDA comments regarding SAP
385	11/24/2015	0201	Request for Type C Meeting
386	12/01/2015	N/A	Email correspondence regarding meeting time for Comments on SAP
387	12/04/2015	N/A	Email correspondence sent to FDA regarding Meeting Request (Type C Mtg)
388	12/08/2015	N/A	Email correspondence from FDA regarding time and date of telecom (Type C Mtg)
389	12/08/2015	N/A	Portola response to FDA email confirming Meeting time and date (Type C Mtg)
390	12/10/2015	N/A	Email from FDA – Courtesy copy of Meeting Request Granted Letter
391	12/10/2015	N/A	Portola response to confirm receipt of Courtesy copy of Meeting Request Granted
392	12/17/2015	N/A	Preliminary responses to meeting questions for Dec 18, 2015 Teleconference Meeting with FDA
393	12/17/2015	N/A	Acknowledgment of preliminary responses to meeting questions for Dec 18, 2015 and additional list of attendees for teleconference
394	12/21/2015	0202	Request for Type C Meeting
395	12/21/2015	0203	Type C Meeting Follow-up Correspondence
396	1/7/2016	0204	Development Safety Update Report (reporting period 01 October 2014 to 30 September 2015)
397	1/7/2016	N/A	Correspondence – FDA provided Meeting Minutes from Dec 18, 2015 Meeting
398	1/8/2016	N/A	Correspondence – Portola's response to FDA regarding Meeting Minutes provided from Dec 18, 2015 meeting - highlighted
399	1/8/2016	N/A	Correspondence – Courtesy copy of meeting granted
400	1/8/2016	N/A	Correspondence – Regarding Request for Proprietary Name

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401	1/12/2016	N/A	Correspondence – FDA request for updated protocol
402	1/12/2016	N/A	Correspondence – Portola response regarding updated protocol
403	1/14/2016	0205	Information Amendment: Statistical Analysis Plan 15-020
404	1/19/2016	N/A	Correspondence - Statistical Comments regarding IND 72679: Betrixaban Maleate Capsules
405	1/21/2016	N/A	Correspondence – Jacqueline Dombroski, provided contact info to FDA
406	1/21/2016	N/A	Correspondence – Acknowledgement of Statistical Comments (19Jan2016) and attached table for protocol and SAP for review
407	1/22/2016	N/A	Correspondence – FDA confirms receipt of Jacqueline's contact info
408	1/26/2016	0206	Response to statistical Comments
409	1/26/2016	N/A	Correspondence – Portola sent email notification to FDA regarding submission of SN0206
410	1/27/2016	N/A	Correspondence – FDA confirms receipt of SN0206
411	1/28/2016	N/A	Correspondence – FDA provided comments on Protocol, Charter and SAP
412	1/29/2016	0207	Protocol Amendment – Change in protocol, including SAP and CEC Charter
413	2/2/2016	N/A	Correspondence – Portola inquired for extension of submission Type C Briefing Document, confirmation by FDA approved
414	2/5/2016	0208	Type C Meeting Briefing Package
415	2/9/2016	N/A	Correspondence – FDA Confirmed receipt of Desk Copies
416	2/22/2016	N/A	Correspondence – Letter from FDA regarding Proprietary Name Request Conditionally Acceptable
417	3/1/2016	N/A	July 25, 2007 – USAN archived 3-1-2016
418	3/1/2016	N/A	Correspondence – Meeting Request, Written Response
419	3/3/2016	0209	Request for Type B Meeting
420	3/7/2016	N/A	Correspondence – FDA provided comments regarding Jan 29, 2016 submission containing the SAP and CEC Charter
421	3/8/2016	N/A	Correspondence – Portola submitted a written e-mail requesting written comments and an urgent telephone call regarding the Information request (Dated 7March2016)
422	3/8/2016	N/A	Correspondence – FDA acknowledged receipt of request via email
423	3/8/2016	N/A	Correspondence – FDA responded to request regarding written comments for Urgent tcon
424	3/8/2016	N/A	Correspondence – Portola confirmed receipt of clarification of Statistical Comments on the APEX SAP

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425	3/8/2016	N/A	Correspondence – Portola responded regarding Request for Written comments
426	3/10/2016	0210	Information Amendment: Statistical Analysis Plan
427	3/14/2016	N/A	Correspondence – Portola notified FDA that SN0210 SAP submission will need to be replaced
428	3/14/2016	N/A	Correspondence – FDA acknowledged receipt of email notification regarding SAP (SN0210)
429	3/15/2016	0211	Information Amendment – Statistical Analysis Plan Resubmission
430	3/15/2016	N/A	Correspondence – Portola notified FDA of Statistical Analysis Plan resubmission, and provided email attachments
431	3/16/2016	N/A	Correspondence – FDA Acknowledged receipt of Statistical Analysis Plan resubmission via email
432	3/23/2016	N/A	Correspondence – FDA (Rabiya Laiq) notified Portola she will be managing the meeting request – meeting granted letter attached
433	3/24/2016	N/A	Correspondence – Portola send March 2016 APEX Topline Data, and requested a Type A meeting
434	3/28/2016	N/A	Correspondence – FDA provided Change in contact information for Ms. Patricia Garvey
435	3/29/2016	N/A	Correspondence – FDA provided Project Manager information to Portola
436	3/29/2016	0212	Submission – Pre- NDA CMC Type B Meeting Briefing Document
437	3/30/2016	N/A	Correspondence – regarding PM info
438	3/30/2016	N/A	Correspondence – FDA responded to Portola regarding missed call
439	3/30/2016	N/A	Correspondence – Portola sent email with content attached for a meeting request
440	3/31/2016	N/A	Correspondence – FDA responded regarding Meeting Request
441	4/01/2016	N/A	Correspondence – FDA/Portola Correspondence regarding question on meeting
442	4/05/2016	N/A	Correspondence – Portola notified Dr. Laiq regarding delivery of briefing books
443	4/05/2016	N/A	Correspondence – Portola notified FDA regarding Meeting Request official submission
444	4/11/2016	0214	Submission – General Correspondence: Authorization to Refer to Portola IND072679
445	4/12/2016	N/A	Correspondence – FDA - Meeting requested Granted
446	4/14/2016	N/A	Correspondence – Portola confirmed to proceed with FDA Meeting granted

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447	4/14/2016	N/A	Correspondence – Inquiry regarding Format for the "Addendum" to Meeting Briefing Info
448	4/23/2016	0216	Submission – Meeting Briefing Document Addendum
449	4/27/2016	0217	Submission – Type C Meeting Request for Guidance, Written Responses
450	4/29/2016	N/A	Correspondence – Foreign Visitor Data Request Form for 11 May 2016 Pre-NDA Meeting (Dr. Cohen)
451	4/29/2016	N/A	Correspondence – Courtesy copy of the official WRO response to meeting package
452	5/2/2016	0218	Submission – Initial Pediatric Study Plan Including a Request for a Partial Waiver and a Deferral
453	5/3/2016	N/A	Correspondence – FDA provided courtesy copy of the Type C guidance meeting granted letter via email
454	5/3/2016	N/A	Correspondence – Portola sent follow-up email confirming receipt of Type C guidance meeting granted letter
455	5/3/2016	N/A	Correspondence – FDA sent email acknowledging receipt of foreign visitor form
456	5/3/2016	N/A	Correspondence – Portola sent email to notify that electronic copy of iPSP was submitted
457	5/4/2016	N/A	Correspondence – Question about 11May Meeting Attendance
458	5/5/2016	N/A	Correspondence – List of Meeting Participants
459	5/5/2016	N/A	Correspondence - Portola send acknowledgment email regarding receivable of Preliminary Responses to questions
460	5/5/2016	N/A	Correspondence – FDA provided courtesy copy of the pre-NDA meeting preliminary comments
461	5/5/2016	N/A	Correspondence – Portola additional participant requested email to FDA
462	5/5/2016	N/A	Correspondence – Response from FDA regarding meeting attendance
463	5/9/2016	N/A	Correspondence – FDA requested meeting slide deck
464	5/9/2016	N/A	Correspondence – Portola sent FDA questions for discussion via email
465	5/9/2016	N/A	Correspondence – schedule visit notification
466	5/10/2016	N/A	Correspondence – FDA sent acknowledgment confirmation of correspondence receipt via email
467	5/10/2016	N/A	Correspondence – Portola provided Final List of Participants, Portola's Slide Deck and Telephone Conference Information
468	5/10/2016	N/A	Correspondence – Portola provided an updated Teleconference information
469	5/11/2016	N/A	Correspondence – FDA provided list of scheduled meeting participants
470	5/11/2016	N/A	Correspondence – Portola provided final Slide Deck to FDA

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471	5/20/2016	N/A	Correspondence – FDA emailed Portola Requesting official submission to the IND of the slidedeck
472	5/20/2016	0219	Submission – Request for Pre-NDA Meeting as Follow-up to Type C, Request for Advice and Type B, APEX Pre-NDA Meeting
473	5/20/2016	N/A	Correspondence – Portola sent email to FDA following up in regards to SN0219 Submission – Request for Pre-NDA Mtg with Statistical and Clinical Reviewers
474	5/23/2016	N/A	Correspondence – ROC with FDA about Request for Pre-NDA Meeting with Statistical and Clinical reviewers
475	5/25/2016	0220	Submission – 11 May 2016 Pre-NDA Meeting Final Slide Deck
476	5/27/2016	N/A	Correspondence – Guidance Meeting Request Granted – courtesy copy
477	5/27/2016	N/A	Correspondence – Courtesy cop of May 11, 2016 meeting minutes
478	6/01/2016	0221	Submission – Request for a meeting: Teleconference to follow-up on the Pre-NDA CMC Meeting Written Responses of 23 April 2016
479	6/03/2016	N/A	Correspondence – FDA Follow up meeting request email
480	6/03/2016	N/A	Correspondence – Portola's response to follow—up meeting request
481	6/07/2016	N/A	Correspondence – Portola sent email to FDA regarding Telephone Conference with OPG 8 June
482	6/07/2016	N/A	Correspondence – Portola provided list of participants and draft slides for 15 June meeting
483	6/8/2016	N/A	Correspondence – Portola sent Follow-up on the Pre-NDA CMC Meeting Written Responses dated 23 April 2016 – Teleconference on 8 June 2016
484	6/10/2016	N/A	Correspondence – FDA Sent list of participants
485	6/10/2016	N/A	Correspondence – FDA sent an email acknowledging receipt of correspondence
486	6/10/2016	N/A	Correspondence – FDA provided Final Written Responses for April 27, 2016 Meeting request
487	6/10/2016	N/A	Correspondence – Portola acknowledged receipt of written responses from FDA
488	6/10/2016	N/A	Correspondence – FDA sent via email courtesy copy of preliminary meeting comments for May 20, 2016 meeting request
489	6/14/2016	0222	Submission – Type C Guidance Meeting Cancellation
490	6/14/2016	N/A	Correspondence – Portola sent email requesting to cancel June 15th meeting

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491	6/15/2016	0223	Submission – Request for Advice Meeting: Follow-up from APEX Pre-NDA Meeting
492	6/15/2016	N/A	Correspondence – FDA provided a courtesy copy of meeting cancellation letter
493	6/15/2016	0224	Submission – Summary Report of Meeting with Office of Product Quality
494	6/26/2016	N/A	Correspondence – Portola sent email regarding Follow-up to 8 June 2016 Meeting
495	6/27/2016	N/A	Correspondence – FDA provided courtesy copy of meeting granted letter
496	6/28/2016	0225	Submission – Follow-up to Meeting Request for Advice on Manufacturing Plans
497	7/07/2016	N/A	Correspondence – Record of Contract: Phone call from Patty Garvy, FDA
498	7/08/2016	N/A	Correspondence – FDA provided courtesy copy of the initial PSP Written Response letter
499	7/11/2016	N/A	Correspondence – FDA provided a copy of the Written Responses to the June 15 Meeting Request
500	7/15/2016	N/A	Correspondence – Portola sent email - Clarifications and Request for Comment on Two Topics Raised in Previous Correspondence with the Division
501	7/28/2016	N/A	Correspondence – Portola sent follow-up email regarding clarification and request for comments on two topics raised in previous correspondence
502	7/29/2016	N/A	Correspondence – Request for Advice on Module 1 of the NDA
503	08/01/2016	0226	Submission – Pediatric Study Plan - other
504	08/01/2016	N/A	Correspondence – FDA provided responses to questions for July 15, 2016 email
505	08/01/2016	N/A	Correspondence – Portola, notified FDA regarding iPSP submission, with courtesy copies
506	08/8/2016	N/A	Correspondence – Acknowledgement of email receipt of iPSP, and notification of Regulatory PM change at FDA
507	08/8/2016	N/A	Correspondence – Portola provided redline version of iPSP to new regulatory PM at FDA
508	08/9/2016	N/A	Correspondence – FDA New regulatory PM acknowledged receipt of iPSP
509	08/15/2016	N/A	Correspondence – FDA Response to Request for Advice on Module 1
510	08/16/2016	N/A	Correspondence – Portola Acknowledged receipt of advice on Module 1

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511	08/17/2016	N/A	Correspondence – FDA Response to request for advice about electronic files for QTc Study, and Compression Ultrasonography in the Phase 3 APEX Study
512	08/17/2016	N/A	Correspondence – Portola acknowledged receipt of advice regarding ECGs and CUS Scans
513	08/17/2016	N/A	Correspondence – Portola sent follow-up to SN0226 Pediatric Study plan – responses to the comments on iPSP
514	08/25/2016	N/A	Correspondence – Record of Contact – Call from FDA about the Status of the iPSP and NDA submission Plan
515	08/26/2016	N/A	Correspondence – FDA Information Request – Responses to Comments on the iPSP
516	08/26/2016	N/A	Correspondence – Portola acknowledged receipt of iPSP Information request from FDA
517	08/29/2016	0227	Submission – Response to Request for Information (PSP Resubmission)
518	09/02/2016	0228	Submission – Responses to FDA's Comments dated 31 August 2016
519	09/06/2016	N/A	Correspondence – FDA Acknowledged receipt of Pediatric Study Plan: Response to FDA's Comments dated 31 August 2016
520	09/18/2016	N/A	Correspondence – Portola – Response to Comments Received 16 September 2016 and Submission of AGREED PSPS
521	09/19/2016	0229	Submission – Responses to FDA's Comments dated 16 September 2016
522	09/20/2016	N/A	Correspondence – FDA – notified Portola to contact Patty Garvey during Thomas's vacation (PSP)
523	09/20/2016	N/A	Correspondence – Portola – Acknowledge email regarding Contact info
524	09/22/2016	N/A	Correspondence – Portola - Request for Status Update about Review Path of Pediatric Study Plan
525	09/22/2016	N/A	Correspondence – Portola – Request for Status Update about Review Path
526	09/23/2016	N/A	Correspondence – FDA – Request for Status Update about Review Path Response from FDA
527	09/26/2016	N/A	Correspondence – FDA – Update that FDA regarding further comments on iPSP
528	09/27/2016	0230	Submission – PSP revised Initial Pediatric Study Plan responses to the FDA's comments dated 27 September 2016
529	09/27/2016	N/A	Correspondence – FDA, Comments to Sponsor (iPSP)
530	09/28/2016	N/A	Correspondence – Portola, notified FDA regarding submission for FDA Comments dated 27 September 2016 I PSP

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531	09/28/2016	N/A	Correspondence – FDA acknowledged notification of submission for FDA Comments dated 27 September 2016 I PSP
532	10/12/2016	N/A	Correspondence – Portola sent Enquiry about Review of the Pediatric Study Plan by PeRC to FDA
533	10/13/2016	N/A	Correspondence – Record of Contact – Regarding Enquiry about Review of the PSP by PeRC
534	10/17/2016	N/A	Correspondence – Portola, follow-up Enquiry regarding Review of the PSP by PeRC
535	10/18/2016	N/A	Correspondence – FDA Responded to Alex Gold regarding Enquiry about Review of the PSP by PeRC
536	10/18/2016	N/A	Correspondence – FDA Responded to Jacqui regarding Enquiry about Review of the PSP by PeRC
537	10/20/2016	N/A	Correspondence – ROC - Called Thomas Iype to Enquire about Likely Timing of Communication about Review of the PSP by PeRC - FDA Letter Expected Friday
538	10/21/2016	N/A	Correspondence – FDA provided Agreed iPSP – Initial Agreement
539	10/21/2016	N/A	Correspondence - Acknowledgement of Receipt of 21 October 2016 Letter Confirming the Agreed Pediatric Study Plan
540	10/24/2016	N/A	Correspondence – FDA Responded to Request for Regulatory Advice
541	10/25/2016	N/A	Correspondence – Portola – submitted Enquiry Regarding Potential Orientation Meeting
542	10/25/2016	N/A	Correspondence – FDA- Responded regarding Enquiry regarding potential orientation meeting
543	10/27/2016	N/A	Correspondence – FDA sent application orientation schedule
544	10/27/2016	N/A	Correspondence – Portola acknowledged receipt of application orientation schedule
545	10/28/2016	N/A	Correspondence – FDA sent NDA Acknowledgement
546	12/08/2016	0231	Submission – Quality Information Amendment – Stability Data for Betrixaban Tablets
547	12/12/2016	0232	Submission – Clinical Information Amendment: Investigators Brochure Edition 09
548	12/15/2016	0233	Submission – Development Safety Update Report 005 (01 October 2015 to 30 September 2016)
549	12/16/2016	0234	Submission – Nonclinical Information Amendment: Study Report
550	12/16/2016	0235	Submission – Clinical Information Amendment: Clinical Safety Report 11-019 (APEX)
551	01/06/2017	0236	Submission – Clinical Information Amendment: New Protocol for Phase 1 Pediatric Study 16-021

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552	02/02/207	COR	Correspondence – FDA – Information Request- Rational Dosing Study 16-021
553	02/21/2017	0237	Submission – Responses to Information Request dated 02 February 2017 (Pediatric Study 16-021)
554	03/31/2017	0238	Submission – Quality Information Amendment: Addition of Information on Drug Substance Manufacturing at Hovione, Cork, Ireland
555	04/14/2017	0239	Submission – Quality Information Amendment: Revision of Information on Drug Product
556	04/16/2017	COR	Correspondence – Portola, Confirmation of Submission of Quality Information Amendment SN0239
557	06/16/2017	COR	Correspondence – FDA - SDN 253/eCTD SQN 236 – New Protocol Deficiency Comments
558	06/19/2017	COR	Correspondence – Ptla - SDN 253/eCTD SQN 236 – New Protocol Deficiency Comments - Confirmation that Portola will submit Protocol Amendment
559	06/19/2017	COR	Correspondence – FDA – Acknowledged receipt SDN 253/eCTD SQN 236 – New Protocol Deficiency Comments - Confirmation that Portola will submit Protocol Amendment
560			
561			