06-23-14



CASE PAT032910A-US-PCT

FILING BY "EXPRESS MAIL" UNDER 37 CFR 1.10

Express Mail Label Number _____ Date of Deposit _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 7,964,592

ISSUED: June 21, 2011

INVENTORS: Garcia-Echeverria et al.

FOR: 2, 4- DI (PHENYLAMINO) PYRIMIDINES USEFUL IN THE TREATMENT OF NEOPLASTIC DISEASES, INFLAMMATORY AND IMMUNE SYSTEM DISORDERS

FDA Copy

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

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

Sir:

Pursuant to 35 U.S.C. § 156 and 37 C.F.R. § 1.710 *et seq.*, Novartis AG ("Applicant"), a Corporation organized under the laws of Switzerland, hereby requests an extension of the patent term due to regulatory review of U.S. Patent No. 7,964,592, which was granted on June 21, 2011.

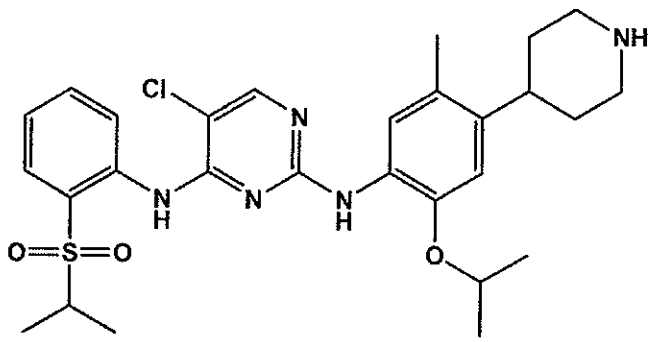
Applicant asserts that it is the owner of the entire right, title and interest in U.S. Patent No. 7,964,592 by virtue of an assignment from the inventors, Garcia-Echeverria et al to Novartis AG. The assignment is recorded in the U.S. Patent and Trademark Office at Reel 024825, Frame 0771. A copy of the assignment is attached hereto as Appendix A. A copy of the Power of Attorney evidencing that Novartis AG being the owner of the entire right, title and interest in and to U.S. Patent No. 7,964,592 appoints Gregory C. Houghton as its agent to act in its interest in this matter is attached hereto as Appendix B.

In accordance with 35 U.S.C. § 156 and 37 C.F.R. § 1.740, Applicant provides the following information in support of its request for a patent term extension. The following sections are numbered analogously to 37 C.F.R. § 1.740.

## 1. Identification of the Approved Product

The approved product is ZYKADIA™ (generic name: ceritinib), a tyrosine kinase inhibitor for oral administration that is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. The active ingredient in ZYKADIA™ , ceritinib, has a chemical name 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine. An alternative chemical name is 5-chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine.

The molecular formula of ceritinib is $C_{28}H_{36}N_5O_3ClS$. The molecular weight of ceritinib is 558.14 g/mole. The chemical structure of ceritinib is:




ZYKADIA™ (ceritinib) is supplied as printed hard-gelatin capsules containing 150 mg of ceritinib and the following inactive ingredients: colloidal anhydrous silica, L-hydroxpropylcellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and hard gelatin capsule shells. The capsule shell is composed of gelatin, indiogotine, and titanium dioxide.

## 2. Identification of the Federal Statute under which Regulatory Review Occurred

The approved product was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, Section 505 (New Drugs).

## 3. The Date of Permission for Commercial Marketing

The approved product received permission for commercial marketing under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355) on April 29, 2014. A copy of the FDA approval letter is attached hereto as Appendix C.

## 4. Active Ingredient Statement

The sole active ingredient in ZYKADIA™ is ceritinib, which 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 prior to the approval of NDA 205755 by the United States Food and Drug Administration on April 29, 2014.

## 5. Statement of Timely Filing

The last day on which this application could be submitted is June 27, 2014, which is 60 days from the approval of NDA 205755 on April 29, 2014. This application is timely filed, because it is being submitted on or prior to June 27, 2014.

## 6. Identification of Patent for which Extension is Sought

This application seeks to extend the term of U.S. Patent No. 7,964,592, which issued June 21, 2011 to Garcia-Echeverria et al., the term of which would otherwise expire on January 13, 2027.

## 7. Patent Copy

A complete copy of U.S. Patent No. 7,964,592, identified in paragraph 6 above, is attached as Appendix D.

## 8. Post-Issuance Activity Statement

No Reexamination certificate, no certificate of correction, no terminal disclaimer, or Reissue has been issued or requested with respect to U.S. Patent No. 7,964,592. No maintenance fees have become due since the patent has issued.

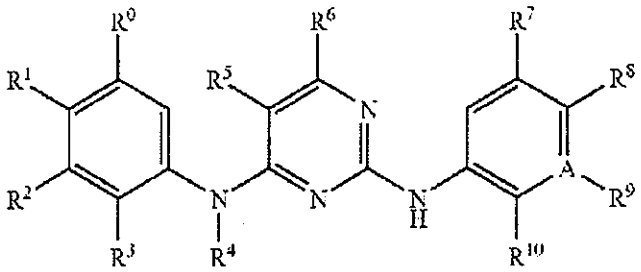
9. **A statement that the patent claims the approved product, or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) the approved product, if the listed claims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

U.S. Patent No. 7,964,592 claims the approved product, a method of manufacturing the approved product, and a method of using the approved product. Claims 1-4, 7-10, 14, and 15 read on the approved product. Claim 13 reads on a method of manufacturing the approved product. Claim 16 reads on a method of using the approved product.

Approved product:

Claim 1. A compound of formula I

(I)



each of $R^0$ or $R^2$ independently is hydrogen, $C_1$-$C_8$alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, $C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, or halogen;

$R^1$ is hydrogen, $C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, $C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted Heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, halogen;

$R^3$ is $C_1$-$C_8$alkylsulfinyl, $C_1$-$C_8$alkylsulfonyl, $C_5$-$C_{10}$ arylsulfonyl, or unsubstituted or substituted carbamoyl;

$R^4$ is hydrogen;

$R^5$ is chloro or bromo;

$R^6$ is hydrogen;

each of $R^7$ and $R^9$ independently is hydrogen, $C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, $C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted carbamoyl, or unsubstituted or substituted sulfamoyl;

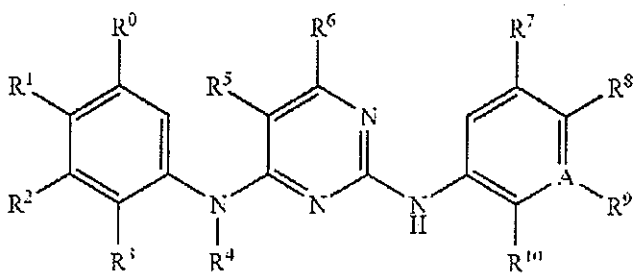
$R^8$ is $C_5$-$C_{10}$aryl; unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S; $C_5$-$C_{10}$aryloxy; unsubstituted or substituted heterocyclyloxy; or unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy; and

$R^{10}$ is $C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, or halogen; and

A is C;

or salts thereof.

Claim 1 reads on the approved product, because ceritinib is the compound of claim 1 when, in formula (I):



each of $R^0$ and $R^2$ is hydrogen;

$R^1$ is hydrogen;

$R^3$ is $C_1$-$C_8$ alkylsulfonyl;

$R^4$ is hydrogen;

$R^5$ is chloro;

$R^6$ is hydrogen;

$R^7$ and $R^9$ are, respectively, $C_1$-$C_8$ alkyl and hydrogen;

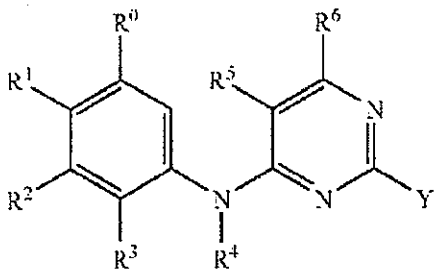
$R^8$ is an unsubstituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O, and S;

$R^{10}$ is $C_1$-$C_8$ alkoxy; and

A is C.

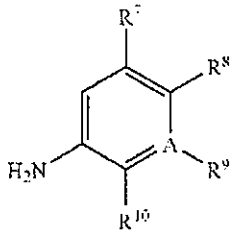
Method of Manufacturing Approved Product:

Claim 13. A process for the production of a compound of formula I according to claim 1, comprising reacting a compound of formula II



(II)

wherein $R^0$, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, and $R^6$ are as defined in claim 1, and Y is a leaving group, with a compound of formula III



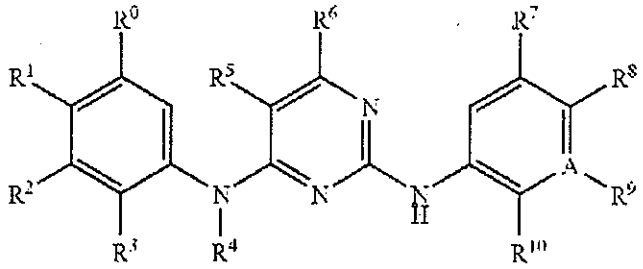
(III)

wherein A, $R^7$, $R^8$, $R^9$ and $R^{10}$ are as defined in claim 1;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined in claim 1, into another compound of formula I as defined in claim 1;

and recovering the resulting compound of formula I in free from or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

Claim 13 reads on a method of manufacturing the approved product, because the compound according to claim 1 (from which claim 13 depends) is ceritinib when, in the compound of formula I:



each of $R^0$ and $R^2$ is hydrogen;

$R^1$ is hydrogen;

$R^3$ is $C_1$-$C_8$ alkylsulfonyl;

$R^4$ is hydrogen;

$R^5$ is chloro;

$R^6$ is hydrogen;

$R^7$ and $R^9$ are, respectively, $C_1$-$C_8$ alkyl and hydrogen;

$R^8$ is an unsubstituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O, and S;

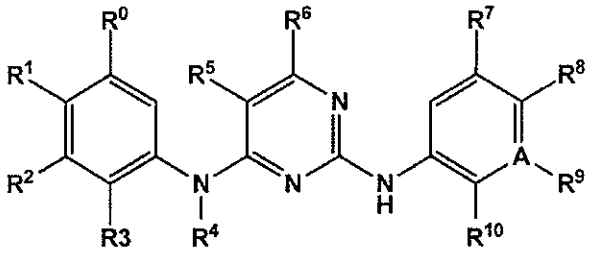
$R^{10}$ is $C_1$-$C_8$ alkoxy; and

A is C.

Method of Using Approved Product:

> Claim 16. A method for the treatment of breast tumors in a subject in need thereof which comprises administering an effective amount of a compound according to claim 1 or a pharmaceutical composition comprising same.

Claim 16 reads on a method of using the approved product, because the compound according to claim 1 (from which claim 16 depends) is ceritinib when, in the compound of formula I:




each of $R^0$ and $R^2$ is hydrogen;

$R^1$ is hydrogen;

$R^3$ is $C_1$-$C_8$ alkylsulfonyl;

$R^4$ is hydrogen;

$R^5$ is chloro;

$R^6$ is hydrogen;

$R^7$ and $R^9$ are, respectively, $C_1$-$C_8$ alkyl and hydrogen;

$R^8$ is an unsubstituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O, and S;

$R^{10}$ is $C_1$-$C_8$ alkoxy; and

A is C.

## 10. Statement of the Relevant Dates to Determine the Regulatory Review Period

The relevant dates and information pursuant to 35 U.S.C. § 156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) The patent for which extension of the term thereof is sought claims a human drug product, a method of manufacturing it, and a method of using it.

(A) An Investigational New Drug Application for ZYKADIA™ (ceritinib) was submitted on October 8, 2010, was assigned IND 109272, and became effective on November 7, 2010. A copy of the Cover letter and FDA form 1571, to verify the submittal date, are attached as Appendix E.

(B) A New Drug Application for ZYKADIA™ (ceritinib) was initially submitted on December 24, 2013 and was assigned NDA No. 205755. A copy of the acknowledgment letter is attached as Appendix F.

(C) NDA No. 205755 was approved on April 29, 2014.

## 11. Brief Description of Activities Undertaken During the Regulatory Review Period

As a brief description of the activities undertaken during the applicable regulatory review period, attached hereto as Appendix G is a chronology of the major communications between the U.S. Food and Drug Administration and the Applicant in IND No. 109272 and NDA No. 205755.

12. **Opinion of Eligibility for Extension**

Applicant is of the opinion that U.S. Patent No. 7,964,592 is eligible for extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.720 because it satisfies all of the requirements for such extension as follows:

(A) 35 U.S.C. § 156(a) and 37 C.F.R. § 1.720(a)

U.S. Patent No. 7,964,592 claims a human drug product, ZYKADIA™ (ceritinib), a method of manufacturing it, and a method of using it.

(B) 35 U.S.C. § 156(a)(1) and 37 C.F.R. § 1.720(g)

The term of U.S. Patent No. 7,964,592 (expiring January 13, 2027) has not expired before the submission of this application.

(C) 35 U.S.C. § 156(a)(2) and 37 C.F.R. § 1.720(b)

The term of U.S. Patent No. 7,964,592 has never been extended under 35 U.S.C. § 156.

(D) 35 U.S.C. § 156(a)(3) and 37 C.F.R. § 1.720(c)

The application for extension of the term of U.S. Patent No. 7,964,592 is submitted by the owner of record thereof in accordance with the requirements of 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740.

(E) 35 U.S.C. § 156(a)(4) and 37 C.F.R. § 1.720(d)

The approved product, ZYKADIA™ (ceritinib), has been subjected to a regulatory review period under 35 U.S.C. § 156(g)(1) before its commercial marketing or use.

(F) 37 C.F.R. § 1.720(h)

No other patent term has been extended for the same regulatory review period for the approved product, ZYKADIA™ (ceritinib).

(G) 35 U.S.C. § 156(a)(5)(A) and 37 C.F.R. § 1.720(e)(1)

The permission for the commercial marketing or use of the approved product, ZYKADIA™ (ceritinib), is the first received permission for commercial marketing or use of

ZYKADIA™ (ceritinib) under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355), the provision of law under which the applicable regulatory review occurred.

**Length of extension claimed under 37 C.F.R. § 1.740(a)(12)**

The length of extension of the patent term of U.S. Patent No. 7,964,592 requested by Applicant is 472 days as limited by the 14 year limit of 35 U.S.C. § 156(c)(3), so that the expiration date will be April 29, 2028. The length of the extension was calculated in accordance with 37 C.F.R. § 1.775 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(1)(B) began on November 7, 2010 and ended on April 29, 2014, amounting to a total of 1271 days which is the sum of (i) and (ii) below:

(i) The period of review under 35 U.S.C. § 156(g)(1)(B)(i), the "Testing Period," began on November 7, 2010 and ended on December 24, 2013 which is 1144 days;

(ii) The period for review under 35 U.S.C. § 156(g)(1)(B)(ii), the "Application Period," began on December 24, 2013 and ended on April 29, 2014, which is 127 days;

(b) The regulatory review period upon which the period for extension is calculated is the entire regulatory review period as determined in subparagraph (a) above (1271 days) less:

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (June 21, 2011), i.e., 227 days, and

(ii) The number of days during which the Applicant did not act with due diligence, i.e., zero days, and

(iii) One-half of the number of days remaining in the period in subparagraph (a)(i) after subtracting the number of days in subparagraphs (b)(i) and (b)(ii), which is one-half of (1144 - [227 + 0]) or 458 days;

which results in a period of 1271 -[227 + 0 + 458 days] = 586 days.

(c) The number of days as determined in subparagraph (b), when added to the original term (January 13, 2027), would result in the date of August 21, 2028.

(d) Fourteen (14) years when added to the date of the NDA Approval Letter (April 29, 2014) would result in the date of April 29, 2028.

(e) The earlier date as determined by subparagraphs (c) and (d) is April 29, 2028.

(f) Since the original patent was issued after September 24, 1984, the extension otherwise obtainable is limited to not more than five (5) years. Five years, when added to the original expiration of U.S. Patent No. 7,964,592 (January 13, 2027), results in the date January 13, 2032.

(g) The earlier date as determined in subparagraphs ((e) and (f) is April 29, 2028.

## 13. Duty of Disclosure Acknowledgement Under 37 C.F.R. § 1.740(a)(13)

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 any information which is material to the determination of entitlement to the extension sought.

## 14. Fee Charge

The prescribed fee for receiving and acting upon this application is to be charged to Applicant's Deposit Account No. 19-0134 as authorized in the attached transmittal letter.

## 15. Correspondence Address Required by 37 C.F.R. § 1.740(a)(15)

All correspondence relating to this application for patent term extension should be addressed to:

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Bldg. 433
East Hanover, NJ 07936-1080

Pursuant to 37 C.F.R. § 1.740(b), two identical copies of this application, with accompanying exhibits, are enclosed. Pursuant to M.P.E.P § 2753, an additional two copies, with accompanying exhibits, are enclosed. Accordingly, a total of four copies and one original application for patent term extension of the United State Patent No. 7,964,592 are submitted herewith.

Respectfully submitted,

Novartis Pharmaceuticals Corp.
Patents Pharma
One Health Plaza, Building 433
East Hanover, NJ 07936-1080

Gregory C. Houghton
Attorney for Applicant
Reg. No. 47,666
(862) 778-5115

Date: 6/20/14

APPENDIX A

United States Patent and Trademark Office



Assignments on the Web > Patent Query

# Patent Assignment Abstract of Title

***NOTE:Results display only for issued patents and published applications. For pending or abandoned applications please consult USPTO staff.***

**Total Assignments: 1**

**Patent #:** 7964592 **Issue Dt:** 06/21/2011 **Application #:** 10549250 **Filing Dt:** 05/18/2006

**Publication #:** 20060247241 **Pub Dt:** 11/02/2006

**Inventors:** Carlos Garcia-Echeverria, Takanori Kanazawa, Eiji Kawahara, Keiichi Masuya et al

**Title:** 2,4-DI (PHENYLAMINO) PYRIMIDINES USEFUL IN THE TREATMENT OF NEOPLASTIC DISEASES, INFLAMMATORY AND IMMUNE SYSTEM DISORDERS

**Assignment: 1**

**Reel/Frame:** 024825/0771 **Recorded:** 08/11/2010 **Pages:** 5

**Conveyance:** ASSIGNMENT OF ASSIGNORS INTEREST (SEE DOCUMENT FOR DETAILS).

**Assignors:**

| | |
|---|---|
| GARCIA-ECHEVERRIA, CARLOS | **Exec Dt:** 08/19/2005 |
| KANAZAWA, TAKANORI | **Exec Dt:** 08/30/2005 |
| KAWAHARA, EIJI | **Exec Dt:** 08/31/2005 |
| MASUYA, KEIICHI | **Exec Dt:** 08/19/2005 |
| MATSUURA, NAOKO | **Exec Dt:** 08/30/2005 |
| MIYAKE, TAKAHIRO | **Exec Dt:** 09/05/2005 |
| OHMORI, OSAMU | **Exec Dt:** 08/30/2005 |
| UMEMURA, ICHIRO | **Exec Dt:** 08/30/2005 |

**Assignee:** NOVARTIS AG
LICHTSTRASSE 35
BASEL, SWITZERLAND 4056

**Correspondent:** NOVARTIS INSTITUTES FOR BIOMEDICAL RESEA
220 MASSACHUSETTS AVENUE
CAMBRIDGE, MA 02139

Search Results as of: 05/15/2014 10:27 AM
If you have any comments or questions concerning the data displayed, contact PRD / Assignments at 571-272-3350. v.2.3.4
Web interface last modified: Jul 8, 2013 v.2.3.4

# APPENDIX B

PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

## POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

| | |
|---|---|
| Application Number | 10/549,250 |
| Filing Date | 16 May 2008 |
| First Named Inventor | Carlos GARCIA-ECHEVERRIA |
| Title | 2,4-Di (phenylamino) pyrimidines useful in |
| Art Unit | 1624 |
| Examiner Name | RAO, Deepak R. |
| Attorney Docket Number | 32910A-US-PCT |

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

*OR*

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

29490

*OR*

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

| Practitioner(s) Name | Registration Number |
|---|---|
| | |
| | |
| | |
| | |

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

*OR*

☐ The address associated with Customer Number:

*OR*

☐ Firm or Individual Name

| | | | | | |
|---|---|---|---|---|---|
| Address | | | | | |
| City | | State | | Zip | |
| Country | | | | | |
| Telephone | | Email | | | |

I am the:

☐ Applicant/Inventor.

*OR*

☒ Assignee of record of the entire interest. See 37 CFR 3.71.
*Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on* _____

**SIGNATURE of Applicant or Assignee of Record**

| | | | |
|---|---|---|---|
| Signature | /Arlene K. Musser/ | Date | 11 August 2010 |
| Name | Arlene K. Musser | Telephone | 617.871.5098 |
| Title and Company | Attorney for Applicant, Novartis Institutes for Biomedical Res | | |

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

*If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.*

APPENDIX C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205755

**ACCELERATED APPROVAL**

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

Please refer to your New Drug Application (NDA) dated December 24, 2013, received December 24, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zykadia (ceritinib) capsules, 150 mg.

We also refer to your presubmissions dated November 27, 2013, and December 12, 2013, and your NDA amendments dated January 8, January 24, January 29 (2), February 3, February 5, February 6, February 10 (2), February 12, February 14 (2), February 18 (2), February 19 (3), February 20 (2), February 21, February 24, February 25, February 26, March 3 (2), March 10, March 12, March 13, March 14, March 18, March 19 (3), March 21, March 26, March 28, April 7, April 8 (2), April 10 (2), April 16, April 24, and April 28, 2014.

This new drug application provides for the use of Zykadia (ceritinib) capsules, for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

## APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of the accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

## 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 and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" 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 container labels that are identical to the immediate container labels submitted on March 14, 2014, 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 – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "Final Printed Carton and Container Labels for approved NDA 205755." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

## ADVISORY COMMITTEE

Your application for ceritinib was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of patients with (ALK)-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib, the application did not raise significant public health questions on the role of the ceritinib for this indication, and outside expertise was not necessary since there were no controversial issues that would benefit from an advisory committee discussion.

## ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval.

We remind you of your postmarketing requirement specified in your submission dated April 10, 2014. This requirement, along with required completion dates, is listed below.

2146-1 Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of ceritinib over standard therapy in adult patients with ALK-rearranged (ALK-positive) metastatic NSCLC who have been previously treated with crizotinib or in adult patients with previously untreated ALK-positive metastatic NSCLC.

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Trial Completion: | April 30, 2019 |
| Final Report Submission: | October 31, 2019 |

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated **"Subpart H Postmarketing Requirement(s)."**

## 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

## POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of:

- a serious risk of toxicity from drug over-exposure when taking Zykadia (ceritinib) capsules with food;
- serious risk of toxicity from drug over-exposure due to impaired hepatic function on the pharmacokinetics of Zykadia (ceritinib) capsules;
- serious risk of toxicity from altered drug exposure due to drug-drug interactions of Zykadia (ceritinib) capsules with substrates of CYP3A4 and CYP2C9; and

- potential toxicity from altered GI absorption of Zykadia (ceritinib) capsules with concomitant gastric acid reducing agents.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2146-2 Conduct a clinical trial to evaluate the systemic exposure and safety of 450 mg Zykadia (ceritinib) taken with a meal and 600 mg Zykadia (ceritinib) taken with a light meal as compared with that of 750 mg Zykadia (ceritinib) taken in the fasted state in metastatic ALK-positive NSCLC patients.

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | October 31, 2014 |
| Interim Analysis Report Submission: | August 31, 2016 |
| Final Report Submission: | September 30, 2017 |

2146-3 Complete a pharmacokinetic trial to determine the appropriate dose of Zykadia (ceritinib) in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Report Submission: | June 30, 2016 |

2146-4 Conduct a clinical trial to evaluate the effect of repeat doses of Zykadia (ceritinib) on the single dose pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | October 31, 2014 |
| Final Report Submission: | March 31, 2017 |

2146-5 Conduct a clinical trial to evaluate the effect of repeat doses of Zykadia (ceritinib) on the single dose pharmacokinetics of warfarin (a sensitive CYP2C9 substrate) in accordance with the FDA Guidance for Industry entitled "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations."

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | October 31, 2014 |
| Final Report Submission: | March 31, 2017 |

2146-6 Conduct a clinical trial to evaluate if proton pump inhibitors, $H_2$-receptor antagonists, and antacids alter the bioavailability of Zykadia (ceritinib) and to determine how to dose Zykadia (ceritinib) with regard to concomitant gastric acid reducing agents.

The timetable you submitted on April 10, 2014, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Final Protocol Submission: | February 28, 2015 |
| Final Report Submission: | March 31, 2016 |

Submit the protocols to your IND 109272, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

## POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2146-7 Submit a revised testing monograph (TM) that will include a water content method and specification for LDK378 drug product (capsule content) as post-approval commitment.

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: April 30, 2014

2146-8 Submit 9 months stability data for the 3 registration stability batches (batches 1010000660, 1010000958 and 1010001326) and up to 24 months for one batch from supportive stability (batch AEUS/2012-0023).

The timetable you submitted on April 10, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: May 16, 2014

Submit chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

## PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three

copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

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

## METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

## REPORTING REQUIREMENTS

We remind you that you must comply with the 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, contact the Regulatory Project Manager for this application within two weeks of receipt of this letter.

## PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action

on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Ms. Karen Boyd, Senior Regulatory Project Manager, at (301) 796-7032.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Container Labeling

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**ZYKADIA™ (ceritinib) capsules, for oral use**
**Initial U.S. Approval: 2014**

### ----------INDICATIONS AND USAGE----------

ZYKADIA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

### ----------DOSAGE AND ADMINISTRATION----------

- 750 mg orally once daily. Administer ZYKADIA on an empty stomach (i.e., do not administer within 2 hours of a meal). (2.1)

### ----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 150 mg (3)

### ----------CONTRAINDICATIONS----------

None (4)

### ----------WARNINGS AND PRECAUTIONS----------

- Severe or Persistent Gastrointestinal Toxicity: Dose modification due to diarrhea, nausea, vomiting or abdominal pain occurred in 38% of patients. Withhold if not responsive to anti-emetics or anti-diarrheals, then dose reduce ZYKADIA. (2.2, 5.1)
- Hepatotoxicity: ZYKADIA can cause hepatotoxicity. Monitor liver laboratory tests at least monthly. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.2, 5.2)
- Interstitial Lung Disease (ILD)/Pneumonitis: Occurred in 4% of patients. Permanently discontinue ZYKADIA in patients diagnosed with treatment-related ILD/pneumonitis. (2.2, 5.3)
- QT Interval Prolongation: ZYKADIA can cause QTc interval prolongation. Monitor electrocardiograms and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.2, 5.4)
- Hyperglycemia: ZYKADIA can cause hyperglycemia. Monitor glucose and initiate or optimize anti-hyperglycemic medications as indicated. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.2, 5.5)
- Bradycardia: ZYKADIA can cause bradycardia. Monitor heart rate and blood pressure regularly. Withhold then dose reduce, or permanently discontinue ZYKADIA. (2.2, 5.6)
- Embryofetal Toxicity: ZYKADIA may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus. (5.7, 8.1, 8.7)

### ----------ADVERSE REACTIONS----------

The most common adverse reactions (incidence of at least 25%) are diarrhea, nausea, elevated transaminases, vomiting, abdominal pain, fatigue, decreased appetite, and constipation. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

### ----------DRUG INTERACTIONS----------

- CYP3A Inhibitors and Inducers: Avoid concurrent use of ZYKADIA with strong CYP3A inhibitors or inducers. If concurrent use of a strong CYP3A inhibitor is unavoidable, reduce the dose of ZYKADIA (2.3, 7.1)
- CYP3A and CYP2C9 Substrates: Avoid concurrent use of ZYKADIA with CYP3A or CYP2C9 substrates with narrow therapeutic indices. (7.2)

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**

**Revised: 4/2014**

## FULL PRESCRIBING INFORMATION: CONTENTS*



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

**FULL PRESCRIBING INFORMATION**

## 1 INDICATIONS AND USAGE

ZYKADIA is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14)]*. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Dosing and Administration

The recommended dose of ZYKADIA is 750 mg orally once daily until disease progression or unacceptable toxicity. Administer ZYKADIA on an empty stomach (i.e., do not administer within 2 hours of a meal) *[see Clinical Pharmacology (12.3)]*.

A recommended dose has not been determined for patients with moderate to severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

If a dose of ZYKADIA is missed, make up that dose unless the next dose is due within 12 hours.

### 2.2 Dose Modifications for Adverse Reactions

Recommendations for dose modifications of ZYKADIA for adverse reactions are provided in Table 1.

Approximately 60% of patients initiating treatment at the recommended dose required at least one dose reduction and the median time to first dose reduction was 7 weeks.

Discontinue ZYKADIA for patients unable to tolerate 300 mg daily.

**Table 1: ZYKADIA Dose Interruption, Reduction, or Discontinuation Recommendations**

| Criteria | ZYKADIA Dosing |
|---|---|
| • ALT or AST elevation greater than 5 times ULN with<br>• total bilirubin elevation **less than or equal to 2 times ULN** | Withhold until recovery to baseline or less than or equal to 3 times ULN, then resume ZYKADIA with a 150 mg dose reduction. |
| • ALT or AST elevation greater than 3 times ULN with<br>• total bilirubin elevation **greater than 2 times ULN** in the absence of cholestasis or hemolysis | Permanently discontinue ZYKADIA. |
| Any Grade treatment-related ILD/pneumonitis | Permanently discontinue ZYKADIA. |
| QTc interval greater than 500 msec on at least 2 separate ECGs | Withhold until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then resume ZYKADIA with a 150 mg dose reduction. |
| QTc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia | Permanently discontinue ZYKADIA. |
| Severe or intolerable nausea, vomiting or diarrhea despite optimal anti-emetic or anti-diarrheal therapy | Withhold until improved, then resume ZYKADIA with a 150 mg dose reduction. |
| Persistent hyperglycemia greater than 250 mg/dL despite optimal anti-hyperglycemic therapy | Withhold until hyperglycemia is adequately controlled, then resume ZYKADIA with a 150 mg dose reduction.<br>If adequate hyperglycemic control cannot be achieved with optimal medical management, discontinue ZYKADIA. |
| Symptomatic bradycardia that is not life-threatening | Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate concomitant medications known to cause bradycardia, and adjust the dose of ZYKADIA. |
| Clinically significant bradycardia requiring intervention or life-threatening bradycardia in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension | Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above.<br>If the concomitant medication can be adjusted or discontinued, resume ZYKADIA with a 150 mg dose reduction, with frequent monitoring. |
| Life-threatening bradycardia in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension | Permanently discontinue ZYKADIA. |
| CTCAE, Common Terminology Criteria for Adverse Events v4.03<br>ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; ILD, interstitial lung disease; ECG, electrocardiogram | |

### 2.3 Dose Modification for Strong CYP3A4 Inhibitors

Avoid concurrent use of strong CYP3A inhibitors during treatment with ZYKADIA *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the ZYKADIA dose by approximately one-third, rounded to the nearest 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the ZYKADIA dose that was taken prior to initiating the strong CYP3A4 inhibitor.

## 3 DOSAGE FORMS AND STRENGTHS

150 mg hard gelatin capsule with opaque blue cap and opaque white body containing a white to off-white powder. The opaque blue cap is marked in black ink with "LDK 150MG" and the opaque white body is marked in black ink with "NVR".

## 4 CONTRAINDICATIONS

None

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Severe or Persistent Gastrointestinal Toxicity

Diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of 255 patients including severe cases in 14% of patients treated with ZYKADIA in Study 1. Dose modification due to diarrhea, nausea, vomiting, or abdominal pain occurred in 38% of patients.

Monitor and manage patients using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as indicated. Based on the severity of the adverse drug reaction, withhold ZYKADIA with resumption at a reduced dose as described in Table 1 *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

### 5.2 Hepatotoxicity

Drug-induced hepatotoxicity occurred in patients treated with ZYKADIA. Elevations in alanine aminotransferase (ALT) greater than 5 times the upper limit of normal (ULN) occurred in 27% of 255 patients in Study 1. One patient (0.4%) required permanent discontinuation due to elevated transaminases and jaundice.

Monitor with liver laboratory tests including ALT, aspartate aminotransferase (AST), and total bilirubin once a month and as clinically indicated, with more frequent testing in patients who develop transaminase elevations. Based on the severity of the adverse drug reaction, withhold ZYKADIA with resumption at a reduced dose, or permanently discontinue ZYKADIA as described in Table 1 *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

### 5.3 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, or fatal ILD/pneumonitis can occur in patients treated with ZYKADIA. In Study 1, pneumonitis was reported in 4% of 255 patients treated with ZYKADIA. CTCAE Grade 3 or 4 ILD/pneumonitis was reported in 3% of patients, and fatal ILD/pneumonitis was reported in 1 patient (0.4%) in Study 1. One percent (1%) of patients discontinued ZYKADIA in Study 1 due to ILD/pneumonitis.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue ZYKADIA in patients diagnosed with treatment-related ILD/pneumonitis *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

### 5.4 QT Interval Prolongation

QTc interval prolongation occurs in patients treated with ZYKADIA. Three percent (3%) of 255 patients experienced a QTc interval increase over baseline greater than 60 msec in Study 1. Across the development program of ZYKADIA, one of 304 patients (less than 1%) treated with ZYKADIA doses ranging from 50 to 750 mg was found to have a QTc greater than 500 msec and 3% of patients had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis suggested that ZYKADIA causes concentration-dependent increases in the QTc interval.

When possible, avoid use of ZYKADIA in patients with congenital long QT syndrome. Conduct periodic monitoring with electrocardiograms (ECGs) and electrolytes in patients with congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or those who are taking medications that are known to prolong the QTc interval. Withhold ZYKADIA in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume ZYKADIA at a reduced dose as described in Table 1. Permanently discontinue ZYKADIA in patients who develop QTc interval prolongation in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.2)]*.

### 5.5 Hyperglycemia

Hyperglycemia can occur in patients receiving ZYKADIA. In Study 1, CTCAE Grade 3–4 hyperglycemia, based on laboratory values, occurred in 13% of 255 patients. There was a 6-fold increase in the risk of CTCAE Grade 3–4 hyperglycemia in patients with diabetes or glucose intolerance and a 2-fold increase in patients taking corticosteroids.

Monitor serum glucose levels as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated. Based on the severity of the adverse drug reaction, withhold ZYKADIA until hyperglycemia is adequately controlled, then resume ZYKADIA at a reduced dose as described in Table 1. If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue ZYKADIA *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

### 5.6 Bradycardia

Bradycardia can occur in patients receiving ZYKADIA. In Study 1, sinus bradycardia, defined as a heart rate of less than 50 beats per minute, was noted as a new finding in 1% of 255 patients. Bradycardia was reported as an adverse drug reaction in 3% of patients in Study 1.

Avoid using ZYKADIA in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of ZYKADIA. Permanently discontinue ZYKADIA for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with a concomitant medication known to cause bradycardia or hypotension, withhold ZYKADIA until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if the concomitant medication can be adjusted or discontinued, resume ZYKADIA at a reduced dose as described in Table 1 upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring *[see Dosage and Administration (2.2) and Adverse Reactions (6)]*.

### 5.7 Embryofetal Toxicity

Based on its mechanism of action, ZYKADIA may cause fetal harm when administered to a pregnant woman. In animal studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose of 750 mg daily caused increases in skeletal anomalies in rats and rabbits. Apprise women of reproductive potential of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for at least 2 weeks following completion of therapy *[see Use in Specific Populations (8.7)]*.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Severe or Persistent Gastrointestinal Toxicity *[see Warnings and Precautions (5.1)]*
- Hepatotoxicity *[see Warnings and Precautions (5.2)]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.3)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.4) and Clinical Pharmacology (12.2)]*
- Hyperglycemia *[see Warnings and Precautions (5.5)]*
- Bradycardia *[see Warnings and Precautions (5.6) and Clinical Pharmacology (12.2)]*

### 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 evaluation of ZYKADIA is based on 255 ALK-positive patients in Study 1 (246 patients with NSCLC and 9 patients with other cancers who received ZYKADIA at a dose of 750 mg daily). The median duration of exposure to ZYKADIA was 6 months. The study population characteristics were: median age 53 years, age less than 65 (84%), female

(53%), Caucasian (63%), Asian (34%), NSCLC adenocarcinoma histology (90%), never or former smoker (97%), ECOG PS 0 or 1 (89%), brain metastasis (49%), and number of prior therapies 2 or more (67%).

Dose reductions due to adverse reactions occurred in 59% of patients treated with ZYKADIA. The most frequent adverse reactions, reported in at least 10% of patients, that led to dose reductions or interruptions were: increased ALT (29%), nausea (20%), increased AST (16%), diarrhea (16%), and vomiting (16%). Serious adverse drug reactions reported in 2% or more of patients in Study 1 were convulsion, pneumonia, ILD/pneumonitis, dyspnea, dehydration, hyperglycemia, and nausea. Fatal adverse reactions in patients treated with ZYKADIA occurred in 5% of patients, consisting of: pneumonia (4 patients), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (1 patient each). Discontinuation of therapy due to adverse reactions occurred in 10% of patients treated with ZYKADIA. The most frequent adverse drug reactions that led to discontinuation in 1% or more of patients in Study 1 were pneumonia, ILD/pneumonitis, and decreased appetite.

Tables 2 and 3 summarize the common adverse reactions and laboratory abnormalities observed in ZYKADIA-treated patients.

**Table 2: Adverse Reactions (>10% for All NCI CTCAE* Grades or ≥2% for Grades 3-4) in ALK-Positive Patients Treated with ZYKADIA in Study 1**

| | ZYKADIA N=255 | |
|---|---|---|
| | All Grades | Grade 3–4 |
| | % | % |
| **Gastrointestinal disorders** | | |
| Diarrhea | 86 | 6 |
| Nausea | 80 | 4 |
| Vomiting | 60 | 4 |
| Abdominal pain[a] | 54 | 2 |
| Constipation | 29 | 0 |
| Esophageal disorder[b] | 16 | 1 |
| **General disorders and administration site conditions** | | |
| Fatigue[c] | 52 | 5 |
| **Metabolism and nutrition disorders** | | |
| Decreased appetite | 34 | 1 |
| **Skin and subcutaneous tissue disorders** | | |
| Rash[d] | 16 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Interstitial lung disease/pneumonitis | 4 | 3 |

*National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)
[a]Abdominal pain (abdominal pain, upper abdominal pain, abdominal discomfort, epigastric discomfort)
[b]Esophageal disorder (dyspepsia, gastroesophageal reflux disease, dysphagia)
[c]Fatigue (fatigue, asthenia)
[d]Rash (rash, maculopapular rash, acneiform dermatitis)

Additional clinically significant adverse reactions occurring in 2% or more of patients treated with ZYKADIA included neuropathy (17%; comprised of paresthesia, muscular weakness, gait disturbance, peripheral neuropathy, hypoesthesia, peripheral sensory neuropathy, dysesthesia, neuralgia, peripheral motor neuropathy, hypotonia, or polyneuropathy), vision disorder (9%; comprised of vision impairment, blurred vision, photopsia, accommodation disorder, presbyopia, or reduced visual acuity), prolonged QT interval (4%), and bradycardia (3%).

**Table 3: Key Laboratory Abnormalities Occurring in >10% (All NCI CTCAE Grades) of ALK-Positive Patients Treated with ZYKADIA in Study 1**

| | ZYKADIA N=255 | |
|---|---|---|
| | All Grades | Grade 3–4 |
| | % | % |
| Hemoglobin decreased | 84 | 5 |
| Alanine transaminase (ALT) increased | 80 | 27 |
| Aspartate transaminase (AST) increased | 75 | 13 |
| Creatinine increased | 58 | 2 |
| Glucose increased | 49 | 13 |
| Phosphate decreased | 36 | 7 |
| Lipase increased | 28 | 10 |
| Bilirubin (total) increased | 15 | 1 |

## 7 DRUG INTERACTIONS

### 7.1 Effect of Other Drugs on Ceritinib

Ceritinib is primarily metabolized by CYP3A4 and is a substrate of the efflux transporter P-glycoprotein (P-gp).

Strong CYP3A Inhibitors

Ketoconazole (a strong CYP3A4/P-gp inhibitor) increased the systemic exposure of ceritinib *[see Clinical Pharmacology (12.3)]*. Avoid concurrent use of strong CYP3A inhibitors during treatment with ZYKADIA. If concomitant use of strong CYP3A inhibitors including certain antivirals (e.g., ritonavir), macrolide antibiotics (e.g., telithromycin), antifungals (e.g., ketoconazole), and nefazodone is unavoidable, reduce the ZYKADIA dose by approximately one-third, rounded to the nearest 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the ZYKADIA dose that was taken prior to initiating the strong CYP3A4 inhibitor.

Do not consume grapefruit and grapefruit juice as they may inhibit CYP3A.

Strong CYP3A Inducers

Rifampin (a strong CYP3A4/P-gp inducer) decreased the systemic exposure of ceritinib *[see Clinical Pharmacology (12.3)]*. Avoid concurrent use of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's Wort) during treatment with ZYKADIA.

### 7.2 Effect of Ceritinib on Other Drugs

Ceritinib may inhibit CYP3A and CYP2C9 at clinical concentrations *[see Clinical Pharmacology (12.3)]*. Avoid concurrent use of CYP3A and CYP2C9 substrates known to have narrow therapeutic indices or substrates primarily metabolized by CYP3A and CYP2C9 during treatment with ZYKADIA. If use of these medications is unavoidable, consider dose reduction of CYP3A substrates with narrow therapeutic indices (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) and CYP2C9 substrates with narrow therapeutic indices (e.g., phenytoin, warfarin).

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Pregnancy Category D**

*Risk Summary*

Based on its mechanism of action, ZYKADIA may cause fetal harm when administered to a pregnant woman. In animal studies, administration of ceritinib to rats and rabbits during organogenesis at maternal plasma exposures below the recommended human dose caused increases in skeletal anomalies in rats and rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to a fetus.

*Animal Data*

In an embryo-fetal development study in which pregnant rats were administered daily doses of ceritinib during organogenesis, dose-related skeletal anomalies were observed at doses as low as 50 mg/kg (less than 0.5-fold the human exposure by AUC at the recommended dose). Findings included delayed ossifications and skeletal variations.

In pregnant rabbits administered ceritinib daily during organogenesis, dose-related skeletal anomalies, including incomplete ossification, were observed at doses equal to or greater than 2 mg/kg/day (approximately 0.015-fold the human exposure by AUC at the recommended dose). A low incidence of visceral anomalies, including absent or malpositioned gallbladder and retroesophageal subclavian cardiac artery, was observed at doses equal to or greater than 10 mg/kg/day (approximately 0.13-fold the human exposure by AUC at the recommended dose). Maternal toxicity and abortion occurred in rabbits at doses of 35 mg/kg or greater. In addition, embryolethality was observed in rabbits at a dose of 50 mg/kg.

### 8.3 Nursing Mothers

It is not known whether ceritinib or its metabolites are present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from ceritinib, advise mothers to discontinue nursing.

### 8.4 Pediatric Use

The safety and effectiveness of ZYKADIA in pediatric patients have not been established.

### 8.5 Geriatric Use

Clinical studies of ZYKADIA did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Of the 255 patients in Study 1 who received ZYKADIA at the recommended dose, 40 (16%) were 65 years or older.

### 8.6 Hepatic Impairment

As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. Dose adjustment is not recommended for patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST) based on results of the population pharmacokinetic analysis *[see Clinical Pharmacology (12.3)]*. A recommended dose has not been determined for patients with moderate to severe hepatic impairment.

### 8.7 Females and Males of Reproductive Potential

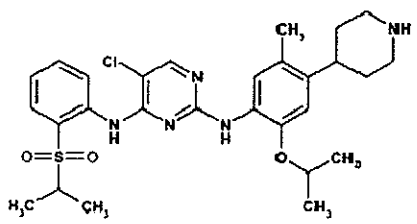
*Contraception*

Based on its mechanism of action, ZYKADIA may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for at least 2 weeks following completion of therapy.

## 11 DESCRIPTION

ZYKADIA (ceritinib) is a tyrosine kinase inhibitor for oral administration. The molecular formula for ceritinib is $C_{28}H_{36}N_5O_3ClS$. The molecular weight is 558.14 g/mole. Ceritinib is described chemically as 5-Chloro-N4-[2-[(1-methylethyl)sulfonyl]phenyl]-N2-[5-methyl-2-(1-methylethoxy)-4-(4-piperidinyl)phenyl]-2,4-pyrimidinediamine.

The chemical structure of ceritinib is shown below:




Ceritinib is a white to almost white or light yellow or light brown powder with a pKa of 9.7 and 4.1.

ZYKADIA is supplied as printed hard-gelatin capsules containing 150 mg of ceritinib and the following inactive ingredients: colloidal anhydrous silica, L-hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and hard gelatin capsule shells. The capsule shell is composed of gelatin, indiogotine, and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Ceritinib is a kinase inhibitor. Targets of ceritinib inhibition identified in either biochemical or cellular assays at clinically relevant concentrations include ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1. Among these, ceritinib is most active against ALK. Ceritinib inhibited autophosphorylation of ALK, ALK-mediated phosphorylation of the downstream signaling protein STAT3, and proliferation of ALK-dependent cancer cells in in vitro and in vivo assays.

Ceritinib inhibited the in vitro proliferation of cell lines expressing EML4-ALK and NPM-ALK fusion proteins and demonstrated dose-dependent inhibition of EML4-ALK-positive NSCLC xenograft growth in mice and rats. Ceritinib exhibited dose-dependent anti-tumor activity in mice bearing EML4-ALK-positive NSCLC xenografts with demonstrated resistance to crizotinib, at concentrations within a clinically relevant range.

### 12.2 Pharmacodynamics

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in an open-label, dose-escalation, and expansion study. A total of 304 patients were treated with ZYKADIA doses ranging from 50 to 750 mg with 255 patients treated with ZYKADIA 750 mg. One of 304 patients (less than 1%) was found to have a QTc greater than 500 msec and 10 patients (3%) had an increase from baseline QTc greater than 60 msec. A central tendency analysis of the QTc data at average steady-state concentrations demonstrated that the upper bound of the 2-sided 90% CI for QTc was 16 msec at ZYKADIA 750 mg. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation *[see Warnings and Precautions (5.4)]*.

Based on central review of ECG data, 2 of 304 patients (0.7%) had bradycardia defined as less than 50 beats per minute. Bradycardia was reported as an adverse drug reaction in 3% of patients in Study 1.

### 12.3 Pharmacokinetics

Absorption

After single oral administration of ZYKADIA in patients, peak plasma levels ($C_{max}$) of ceritinib were achieved at approximately 4 to 6 hours, and area under the curve (AUC) and $C_{max}$ increased dose proportionally over 50 to 750 mg. The absolute bioavailability of ZYKADIA has not been determined.

Following ZYKADIA 750 mg once daily dosing, steady-state was reached by approximately 15 days with a geometric mean accumulation ratio of 6.2 after 3 weeks. Systemic exposure increased in a greater than dose proportional manner after repeat doses of 50 to 750 mg once daily.

Systemic exposure of ceritinib was increased when administered with a meal. A food effect study conducted in healthy subjects with a single 500 mg ceritinib dose showed that a high-fat meal (containing approximately 1000 calories and 58 grams of fat) increased ceritinib AUC by 73% and $C_{max}$ by 41% and a low-fat meal (containing approximately 330 calories and 9 grams of fat) increased ceritinib AUC by 58% and $C_{max}$ by 43% as compared with the fasted state. A 600 mg or higher ZYKADIA dose taken with a meal is expected to result in systemic exposure exceeding that of a 750 mg ZYKADIA dose taken in the fasted state, and may increase adverse drug reactions.

Distribution

Ceritinib is 97% bound to human plasma proteins, independent of drug concentration. The apparent volume of distribution ($V_d/F$) is 4230 L following a single 750 mg ZYKADIA dose in patients. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean in vitro blood-to-plasma ratio of 1.35.

Elimination

Following a single 750 mg ZYKADIA dose, the geometric mean apparent plasma terminal half-life ($t_{1/2}$) of ceritinib was 41 hours in patients. Ceritinib demonstrates nonlinear PK over time. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 L/h) after 750 mg daily dosing than after a single 750 mg dose (88.5 L/h).

*Metabolism:* In vitro studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of ceritinib. Following oral administration of a single 750 mg radiolabeled ceritinib dose, ceritinib as the parent compound was the main circulating component (82%) in human plasma.

*Excretion:* Following oral administration of a single 750 mg radiolabeled ceritinib dose, 92.3% of the administered dose was recovered in the feces (with 68% as unchanged parent compound) while 1.3% of the administered dose was recovered in the urine.

Specific Populations

*Age, Gender, Race, and Body Weight:* Age, gender, race, and body weight had no clinically important effect on the systemic exposure of ceritinib based on population pharmacokinetic analyses.

*Hepatic Impairment:* As ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in patients with hepatic impairment has not been conducted. Based on a population pharmacokinetic analysis of 48 patients with mild hepatic impairment (total bilirubin less than or equal to ULN and AST greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN and any AST) and 254 patients with normal hepatic function (total bilirubin less than or equal to ULN and AST less than or equal to ULN), ceritinib exposures were similar in patients with mild hepatic impairment and normal hepatic function. The pharmacokinetics of ceritinib has not been studied in patients with moderate to severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

*Renal Impairment:* A pharmacokinetic trial in patients with renal impairment has not been conducted as ceritinib elimination via the kidney is low (1.3% of a single oral administered dose). Based on a population pharmacokinetic analysis of 97 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 22 patients with moderate renal impairment (CLcr 30 to less than 60 mL/min) and 183 patients with normal renal function (greater than or equal to 90 mL/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function. Patients with severe renal impairment (CLcr less than 30 mL/min) were not included in the clinical trial.

*Pediatrics:* No trials have been conducted to evaluate the pharmacokinetics of ceritinib in pediatric patients.

Drug Interactions

*Effect of Strong CYP3A Inhibitors on Ceritinib:* In vitro studies show that ceritinib is a substrate of CYP3A. Coadministration of a single 450 mg ZYKADIA dose with ketoconazole (a strong CYP3A inhibitor) 200 mg twice daily for 14 days increased ceritinib AUC (90% CI) by 2.9-fold (2.5, 3.3) and $C_{max}$ (90% CI) by 22% (7%, 39%) in 19 healthy subjects *[see Drug Interactions (7.1)]*. The steady-state AUC of ceritinib at reduced doses after coadministration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone *[see Dosage and Administration (2.3)]*.

*Effect of Strong CYP3A Inducers on Ceritinib:* Coadministration of a single 750 mg ZYKADIA dose with rifampin (a strong CYP3A inducer) 600 mg daily for 14 days decreased ceritinib AUC (90% CI) by 70% (61%, 77%) and $C_{max}$ (90% CI) by 44% (24%, 59%) in 19 healthy subjects *[see Drug Interactions (7.1)]*.

*Effect of Ceritinib on CYP Substrates:* Based on in vitro data, ceritinib may inhibit CYP3A and CYP2C9 at clinical concentrations *[see Drug Interactions (7.2)]*. Time-dependent inhibition of CYP3A was also observed.

*Effect of Transporters on Ceritinib Disposition:* Ceritinib is a substrate of efflux transporter P-gp, but is not a substrate of Breast Cancer Resistance Protein (BCRP), Multidrug Resistance Protein (MRP2), Organic Cation Transporter (OCT1), Organic Anion Transporter (OAT2), or Organic Anion Transporting Polypeptide (OATP1B1) in vitro. Drugs that inhibit P-gp may increase ceritinib concentrations.

*Effect of Ceritinib on Transporters:* Based on in vitro data, ceritinib does not inhibit apical efflux transporters, P-gp, BCRP, or MRP2, hepatic uptake transporters OATP1B1 and OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or organic cation uptake transporters OCT1 and OCT2 at clinical concentrations.

*Effect of Gastric Acid Reducing Agents on Ceritinib:* Gastric acid reducing agents (e.g., proton pump inhibitors, $H_2$-receptor antagonists, antacids) may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases in vitro. A dedicated study has not been conducted to evaluate the effect of gastric acid reducing agents on the bioavailability of ceritinib.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with ceritinib.

Ceritinib was not mutagenic in vitro in the bacterial reverse mutation (Ames) assay but induced numerical aberrations (aneugenic) in the in vitro cytogenetic assay using human lymphocytes, and micronuclei in the in vitro micronucleus test using TK6 cells. Ceritinib was not clastogenic in the in vivo rat micronucleus assay.

There are no data on the effect of ceritinib on human fertility. Fertility/early embryonic development studies were not conducted with ceritinib. There were no adverse effects on male or female reproductive organs in general toxicology studies conducted in monkeys and rats at exposures equal to or greater than 0.5- and 1.5-fold, respectively, of the human exposure by AUC at the recommended dose of 750 mg.

### 13.2 Animal Toxicology and/or Pharmacology

Target organs in nonclinical animal models included, but were not limited to, the pancreas, biliopancreatic/bile ducts, gastrointestinal tract, and liver. Pancreatic focal acinar cell atrophy was observed in rats at 1.5-fold the human exposure by AUC at the recommended dose. Biliopancreatic duct and bile duct necrosis was observed in rats at exposures equal to or greater than 5% of the human exposure by AUC at the recommended dose. Bile duct inflammation and vacuolation were also noted in monkeys at exposures equal to or greater than 0.5-fold the human exposure by AUC at the recommended dose. Frequent minimal necrosis and hemorrhage of the duodenum was exhibited in monkeys at 0.5-fold the human exposure by AUC, and in rats at an exposure similar to that observed clinically.

Ceritinib crossed the blood brain barrier in rats with a brain-to-blood exposure ($AUC_{inf}$) ratio of approximately 15%.

## 14 CLINICAL STUDIES

The efficacy of ZYKADIA was established in a multicenter, single-arm, open-label clinical trial (Study 1). A total of 163 patients with metastatic ALK-positive NSCLC who progressed while receiving or were intolerant to crizotinib were enrolled. All patients received ZYKADIA at a dose of 750 mg once daily. The major efficacy outcome measure was objective response rate (ORR) according to RECIST v1.0 as evaluated by both investigators and a Blinded Independent Central Review Committee (BIRC). Duration of response (DOR) was an additional outcome measure.

The study population characteristics were: median age 52 years, age less than 65 (87%), female (54%), Caucasian (66%), Asian (29%), never or former smoker (97%), ECOG PS 0 or 1 (87%), progression on previous crizotinib (91%), number of prior therapies 2 or more (84%), and adenocarcinoma histology (93%). Sites of extra-thoracic metastasis included brain (60%), liver (42%), and bone (42%). ALK-positivity was verified retrospectively by review of local test results for 99% of patients.

Efficacy results from Study 1 are summarized in Table 4.

**Table 4: Overall Response Rate and Duration of Response[1] in Patients with ALK-Positive NSCLC who Received Prior Crizotinib in Study 1**

| Efficacy Parameter | Investigator Assessment (N=163) | BIRC Assessment (N=163) |
|---|---|---|
| Overall Response Rate (95% CI) | 54.6% (47, 62) | 43.6% (36, 52) |
| CR | 1.2% | 2.5% |
| PR | 53.4% | 41.1% |
| Duration of Response, median (months) (95% CI) | 7.4 (5.4, 10.1) | 7.1 (5.6, NE) |

[1]Overall Response Rate and Duration of Response determined by RECIST v1.0
BIRC, blinded independent review committee; CR, complete response; NE, not estimable; PR, partial response.

The analysis by the BIRC assessment was similar to the analysis by the investigator assessment.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

ZYKADIA 150 mg capsules

Hard gelatin capsule with opaque blue cap and opaque white body; opaque blue cap marked in black ink with "LDK 150MG", opaque white body marked in black ink with "NVR". Available in:

Bottles of 70 capsules.....NDC 0078-0640-70

Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

## 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Inform patients that diarrhea, nausea, vomiting, and abdominal pain are the most commonly reported adverse reactions in patients treated with ZYKADIA. Inform patients of supportive care options such as anti-emetic and anti-diarrheal medications. Advise patients to contact their healthcare provider for severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.1)]*.
- Inform patients of the signs and symptoms of hepatotoxicity. Advise patients to contact their healthcare provider immediately for signs or symptoms of hepatotoxicity *[see Warnings and Precautions (5.2)]*.
- Inform patients of the risks of severe or fatal ILD/pneumonitis. Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.3)]*.
- Inform patients of the risks of QTc interval prolongation and bradycardia. Advise patients to contact their healthcare provider immediately to report new chest pain or discomfort, changes in heartbeat, palpitations, dizziness, lightheadedness, fainting, and changes in or new use of heart or blood pressure medications *[see Warnings and Precautions (5.4, 5.6)]*.
- Inform patients of the signs and symptoms of hyperglycemia. Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperglycemia *[see Warnings and Precautions (5.5)]*.
- Advise females to inform their healthcare provider if they are pregnant. Inform females of reproductive potential of the risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ZYKADIA and for at least 2 weeks following completion of therapy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1, 8.7)]*.
- Advise females not to breastfeed during treatment with ZYKADIA *[see Use in Specific Populations (8.3)]*.
- Inform patients not to consume grapefruit and grapefruit juice during treatment with ZYKADIA *[see Drug Interactions (7.1)]*.

- Take ZYKADIA on an empty stomach (i.e., do not take within 2 hours of a meal) *[see Dosage and Administration (2.1)]*.
- Advise patients to make up a missed dose of ZYKADIA unless the next dose is due within 12 hours *[see Dosage and Administration (2.1)]*.

T2014-XX

**PATIENT INFORMATION**

**ZYKADIA™ (zye kaye' dee ah)**

**(ceritinib) capsules**

**What is the most important information I should know about ZYKADIA?**

**ZYKADIA may cause serious side effects, including:**

**Stomach and intestinal (gastrointestinal) problems.** ZYKADIA causes stomach and intestinal problems in most people, including diarrhea, nausea, vomiting, and stomach-area pain. These problems can sometimes be severe. Follow your healthcare provider's instructions about taking medicines to help these symptoms. Call your healthcare provider for advice if your symptoms are severe or do not go away.

**Liver problems.** ZYKADIA may cause liver injury. Your healthcare provider should do blood tests at least every month to check your liver while you are taking ZYKADIA. Tell your healthcare provider right away if you get any of the following:

- you feel tired
- your skin or the whites of your eyes turn yellow
- you have a decreased appetite
- your urine turns dark or brown (tea color)
- you have itchy skin
- you have nausea or vomiting
- you have pain on the right side of your stomach-area
- you bleed or bruise more easily than normal

**Lung problems (pneumonitis).** ZYKADIA may cause severe or life-threatening swelling (inflammation) of the lungs during treatment that can lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you have any new or worsening symptoms, including:

- trouble breathing or shortness of breath
- fever
- cough with or without mucous
- chest pain

**Heart problems.** ZYKADIA may cause very slow, very fast, or abnormal heartbeats. Your healthcare provider may check your heart during treatment with ZYKADIA. Tell your healthcare provider right away if you feel new chest pain or discomfort, dizziness or lightheadedness, if you faint, or have abnormal heartbeats. Tell your healthcare provider if you start to take or have any changes in heart or blood pressure medicines.

**See "What are possible side effects of ZYKADIA?" for more information about side effects.**

**What is ZYKADIA?**

ZYKADIA is a prescription medicine that is used to treat people with non-small cell lung cancer (NSCLC) that:

- is caused by a defect in a gene called anaplastic lymphoma kinase (ALK), and
- has spread to other parts of the body, and
- who have taken the medicine crizotinib, but their NSCLC worsened or they cannot tolerate taking crizotinib.

It is not known if ZYKADIA is safe and effective in children.

**What should I tell my healthcare provider before taking ZYKADIA?**

Before you take ZYKADIA, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- have diabetes or high blood sugar
- have heart problems, including a condition called long QT syndrome
- are pregnant or plan to become pregnant. ZYKADIA may harm your unborn baby. Women who are able to become pregnant should use an effective method of birth control during treatment with ZYKADIA and for at least 2 weeks after stopping ZYKADIA. Talk to your healthcare provider about birth control methods that may be right for you.
- are breastfeeding or plan to breastfeed. It is not known if ZYKADIA passes into your breast milk. You should not breastfeed if you take ZYKADIA.

**Tell your healthcare provider about all the medicines you take, including** prescription medicines, over-the-counter medicines, vitamins, and herbal supplements.

**How should I take ZYKADIA?**

- Take ZYKADIA exactly as your healthcare provider tells you. Do not change your dose or stop taking unless your healthcare provider tells you to.
- Take ZYKADIA 1 time each day.
- Take ZYKADIA on an empty stomach, do not eat for 2 hours before and do not eat for 2 hours after taking ZYKADIA.
- If you miss a dose of ZYKADIA, take it as soon as you remember. If your next dose is due within 12 hours, then skip the missed dose. Just take the next dose at your regular time.

**What should I avoid while taking ZYKADIA?**

- You should not drink grapefruit juice or eat grapefruit during treatment with ZYKADIA. It may make the amount of ZYKADIA in your blood increase to a harmful level.

**What are the possible side effects of ZYKADIA?**

**ZYKADIA may cause serious side effects, including:**

- **See "What is the most important information I should know about ZYKADIA?"**
- **High blood sugar (hyperglycemia).** People who have diabetes or glucose intolerance or who take a corticosteroid medicine have an increased risk of high blood sugar with ZYKADIA. Follow your healthcare provider's instructions about monitoring your blood sugar. Call your healthcare provider right away if you have any symptoms of high blood sugar, including:
  - increased thirst
  - increased hunger
  - headaches
  - trouble thinking or concentrating
  - urinating often
  - blurred vision
  - tiredness
  - your breath smells like fruit

The most common side effects of ZYKADIA include:

- stomach and intestinal (gastrointestinal) problems. **See "What is the most important information I should know about ZYKADIA?"**
- tiredness, decreased appetite, and constipation

These are not all of the possible side effects of ZYKADIA. For more information, ask your healthcare provider or pharmacist. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**How should I store ZYKADIA?**

- Store ZYKADIA at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep ZYKADIA and all medicines out of the reach of children.**

**General information about the safe and effective use of ZYKADIA**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ZYKADIA for a condition for which it was not prescribed. Do not give it to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for more information about ZYKADIA.

**What are the ingredients in ZYKADIA?**

**Active ingredient:** ceritinib

**Inactive ingredients:** colloidal anhydrous silica, L-hydroxypropylcellulose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate

**Capsule shell contains:** gelatin, indiogotine, and titanium dioxide

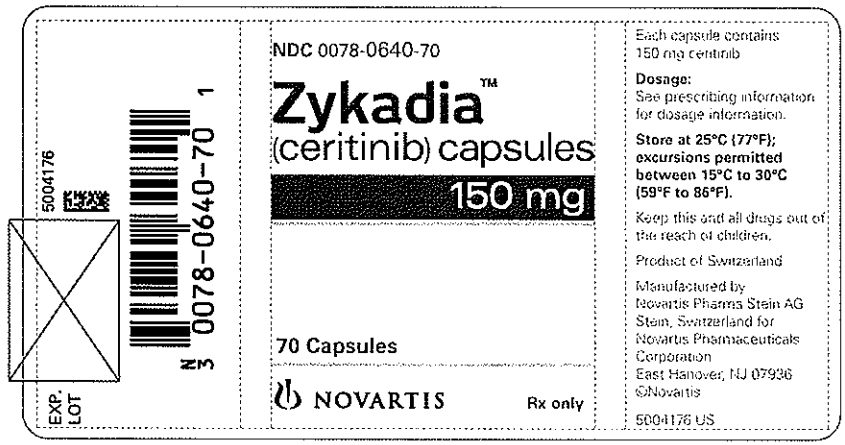
Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

For more information, go to www.US.ZYKADIA.com or call 888-669-6682.

This Patient Information has been approved by the U.S. Food and Drug Administration.

T2014-XX/T2014-XX

Issued: April 2014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Zykadia™
(ceritinib) capsules
150 mg
70 Capsules
NOVARTIS
Rx only
Each capsule contains 150 mg ceritinib
Dosage:
See prescribing information for dosage information.
Store at 25°C (77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).
Keep this and all drugs out of the reach of children.
Product of Switzerland
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Novartis Pharma Stein AG
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East Hanover, NJ 07936
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RICHARD PAZDUR
04/29/2014

APPENDIX D

US007964592B2

(12) **United States Patent**
**Garcia-Echeverria et al.**

(10) **Patent No.: US 7,964,592 B2**
(45) **Date of Patent: Jun. 21, 2011**

(54) **2,4-DI (PHENYLAMINO) PYRIMIDINES USEFUL IN THE TREATMENT OF NEOPLASTIC DISEASES, INFLAMMATORY AND IMMUNE SYSTEM DISORDERS**

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(73) Assignee: **Novartis AG**, Basel (CH)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 1037 days.

(21) Appl. No.: **10/549,250**

(22) PCT Filed: **Mar. 12, 2004**

(86) PCT No.: **PCT/EP2004/002616**

§ 371 (c)(1),
(2), (4) Date: **May 18, 2006**

(87) PCT Pub. No.: **WO2004/080980**

PCT Pub. Date: **Sep. 23, 2004**

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Aug. 15, 2003 (GB) ..... 0319227.5
Sep. 24, 2003 (GB) ..... 0322370.8

(51) **Int. Cl.**
***C07D 239/48*** (2006.01)
***A61K 31/506*** (2006.01)

(52) **U.S. Cl.** ..... **514/227.5**; 514/235.8; 514/249; 514/252.14; 514/275; 544/60; 544/122; 544/295; 544/323

(58) **Field of Classification Search** ..... 544/323, 544/60, 122, 295; 514/275, 227.5, 235.8, 514/249, 252.14
See application file for complete search history.

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*Primary Examiner* — Deepak Rao

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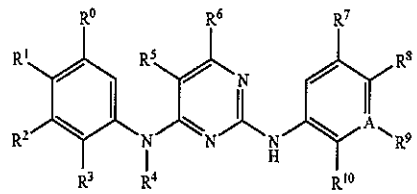
(57) **ABSTRACT**

Novel pyrimidine derivatives of formula I



(I)

to process for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

**17 Claims, No Drawings**

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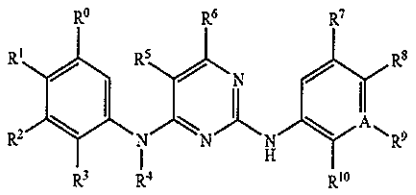
# 2,4-DI (PHENYLAMINO) PYRIMIDINES USEFUL IN THE TREATMENT OF NEOPLASTIC DISEASES, INFLAMMATORY AND IMMUNE SYSTEM DISORDERS

This application is a 371 of PCT/EP04/02616 filed Mar. 12, 2004.

The present invention relates to novel pyrimidine derivatives, to processes for their production, their use as pharmaceuticals and to pharmaceutical compositions comprising them.

More particularly the present invention provides in a first aspect, a compound of formula I



(I)

wherein

each of $R^0$, $R^1$, $R^2$, and $R^3$ independently is hydrogen, $C_1$-$C_8$alkyl, $C_2$-$C_8$alkenyl, $C_2$-$C_8$alkinyl, $C_3$-$C_8$cycloalkyl, $C_3$-$C_8$cycloalkyl$C_1$-$C_8$alkyl, $C_5$-$C_{10}$aryl$C_1$-$C_8$alkyl, hydroxy$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl, amino$C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, $C_1$-$C_8$alkoxy, hydroxy$C_1$-$C_8$alkoxy, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkoxy, halo$C_1$-$C_8$alkoxy, unsubstituted or substituted $C_5$-$C_{10}$aryl$C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, $C_1$-$C_8$alkylthio, $C_1$-$C_8$alkylsulfinyl, $C_1$-$C_8$alkylsulfonyl, $C_5$-$C_{10}$arylsulfonyl, halogen, carboxy, $C_1$-$C_8$alkoxycarbonyl, unsubstituted or substituted carbamoyl, unsubstituted or substituted sulfamoyl, cyano or nitro;

or $R^0$ and $R^1$, $R^1$ and $R^2$, and/or $R^2$ and $R^3$ form, together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

$R^4$ is hydrogen or $C_1$-$C_8$alkyl;

each of $R^5$ and $R^6$ independently is hydrogen, $C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy, halogen, carboxy, $C_1$-$C_8$alkoxycarbonyl, unsubstitued or substituted carbamoyl, cyano, or nitro;

each of $R^7$, $R^8$, $R^9$, and $R^{10}$ independently is $C_1$-$C_8$alkyl, $C_2$-$C_8$alkenyl, $C_2$-$C_8$alkinyl, $C_3$-$C_8$cycloalkyl, $C_3$-$C_8$cycloalkyl$C_1$-$C_8$alkyl, $C_5$-$C_{10}$aryl$C_1$-$C_8$alkyl, hydroxy$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl, amino$C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S, hydroxy, $C_1$-$C_8$alkoxy, hydroxy$C_1$-$C_8$alkoxy, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkoxy, halo$C_1$-$C_8$alkoxy, unsubstituted or substituted $C_5$-$C_{10}$aryl$C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyloxy, or unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, unsubstiued or substituted amino, $C_1$-$C_8$alkylthio, $C_1$-$C_8$alkylsulfinyl, $C_1$-$C_8$alkylsulfonyl, $C_5$-$C_{10}$arylsulfonyl, halogen, carboxy, $C_1$-$C_8$alkoxycarbonyl, unsubstitued or substituted carbamoyl, unsubstitued or substituted sulfamoyl, cyano or nitro; wherein $R^7$, $R^8$ and $R^9$ independently of each other can also be hydrogen;

or $R^7$ and $R^8$, $R^8$ and $R^9$, and/or $R^9$ and $R^{10}$ form together with the carbon atoms to which they are attached, a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S;

A is C or N, most preferably C;

and salts thereof.



The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated:

Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Any asymmetric carbon atoms may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. The compounds may thus be present as mixtures of isomers or as pure isomers, preferably as enantiomer-pure diastereomers.

The invention relates also to possible tautomers of the compounds of formula I.

$C_1$-$C_8$alkyl denotes a an alkyl radical having from 1 up to 8, especially up to 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching; preferably, $C_1$-$C_8$alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or methyl; especially methyl, propyl or tert-butyl.

$C_2$-$C_8$alkenyl denotes a an alkenyl radical having from 2 up to 8, especially up to 5 carbon atoms, the radicals in question being either linear or branched with single or multiple branching; preferably, $C_2$-$C_8$alkenyl is pentenyl, such as 3-methyl-2-buten-2-yl, butenyl, such as 1- or 2-butenyl or 2-buten-2-yl, propenyl, such as 1-propenyl or allyl, or vinyl.

$C_2$-$C_8$alkinyl denotes a an alkinyl radical having from 2 up to 8, especially up to 5 carbon atoms, the radicals in question being either linear or branched; preferably, $C_2$-$C_8$alkinyl is propinyl, such as 1-propinyl or propargyl, or acetylenyl.

$C_3$-$C_8$cycloalkyl denotes a cycloalkyl radical having from 3 up to 8 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, preferably cyclopropyl, cyclopentyl or cyclohexyl.

$C_1$-$C_8$alkoxy is especially methoxy, ethoxy, isopropyloxy, or tert-butoxy.

Hydroxy$C_1$-$C_8$alkyl is especially hydroxymethyl, 2-hydroxyethyl or 2-hydroxy-2-propyl.

Hydroxy$C_1$-$C_8$alkoxy is especially 2-hydroxyethoxy or 3-hydroxypropoxy.

$C_1$-$C_8$alkoxy$C_1$-$C_8$alkoxy is especially 2-methoxyethoxy.

$C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl is especially methoxymethyl, 2-methoxyethyl or 2-ethoxyethyl.

Halogen is preferably fluorine, chlorine, bromine, or iodine, especially fluorine, chlorine, or bromine.

Halo$C_1$-$C_8$alkyl is preferably chloro$C_1$-$C_8$alkyl or fluoro$C_1$-$C_8$alkyl, especially trifluoromethyl or pentafluoroethyl.

Halo$C_1$-$C_8$alkoxy is preferably chloro$C_1$-$C_8$alkoxy or fluoro$C_1$-$C_8$alkoxy, especially trifluoromethoxy.

$C_1$-$C_8$alkoxycarbonyl is especially tert-butoxycarbonyl, iso-propoxycarbonyl, methoxycarbonyl or ethoxycarbonyl.

Unsubstitued or substituted carbamoyl is carbamoyl substituted by one or two substituents selected from hydrogen, $C_1$-$C_8$alkyl, $C_2$-$C_8$alkenyl, $C_2$-$C_8$alkinyl, $C_3$-$C_8$cycloalkyl, $C_3$-$C_8$cycloalkyl$C_1$-$C_8$alkyl, $C_5$-$C_{10}$aryl$C_1$-$C_8$alkyl, hydroxy$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstitued or substituted $C_5$-$C_{10}$aryl, or amino$C_1$-

$C_8$alkyl, or carbamoyl wherein the substituents and the nitrogen atom of the carbamoyl group represent a 5 or 6 membered heterocyclyl further comprising 0, 1 or 2 hetero atoms selected from N, O and S; and is preferably carbamoyl, methylcarbamoyl, dimethylcarbamoyl, propylcarbamoyl, hydroxyethyl-methyl-carbamoyl, di(hydroxyethyl)carbamoyl, dimethylaminoethylcarbamoyl, or pyrrolidinocarbonyl, piperidinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, especially carbamoyl or dimethylcarbamoyl.

Unsubstituted or substituted sulfamoyl is sulfamoyl substituted by one or two substituents selected from hydrogen, $C_1$-$C_8$alkyl, $C_2$-$C_8$alkenyl, $C_2$-$C_8$alkinyl, $C_3$-$C_8$cycloalkyl, $C_3$-$C_8$cycloalkyl$C_1$-$C_8$alkyl, $C_1$-$C_{10}$aryl$C_1$-$C_8$alkyl, hydroxy$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, or amino$C_1$-$C_8$alkyl, or sulfamoyl wherein the substituents and the nitrogen atom of the sulfamoyl group represent a 5 or 6 membered heterocyclyl further comprising 0, 1 or 2 hetero atoms selected from N, O and S; and is preferably sulfamoyl, methylsulfamoyl, propylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylaminoethylsulfamoyl, dimethylsulfamoyl, hydroxyethyl-methyl-sulfamoyl, di(hydroxyethyl)sulfamoyl, or pyrrolidinosulfonyl, piperidinosulfonyl, N-methylpiperazinosulfonyl or morpholinosulfonyl, especially sulfamoyl or methylsulfamoyl.

Unsubstituted or substituted amino is amino substituted by one or two substituents selected from hydrogen, $C_1$-$C_8$alkyl, $C_2$-$C_8$alkenyl, $C_2$-$C_8$alkinyl, $C_3$-$C_8$cycloalkyl, $C_3$-$C_8$cycloalkyl$C_1$-$C_8$alkyl, $C_5$-$C_{10}$aryl$C_1$-$C_8$alkyl, hydroxy$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, amino$C_1$-$C_8$alkyl, acyl, e.g. formyl, $C_1$-$C_8$alkylcarbonyl, $C_5$-$C_{10}$arylcarbonyl, $C_1$-$C_8$alkylsulfonyl or $C_5$-$C_{10}$arylsulfonyl, and is preferably amino, methylamino, dimethylamino, propylamino, benzylamino, hydroxyethyl-methyl-amino, di(hydroxyethyl)amino, dimethylaminoethylamino, acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, especially amino or dimethylamino.

Amino$C_1$-$C_8$alkyl is especially aminoethyl, methylaminoethyl, dimethylaminoethyl or dimethylaminopropyl.

Unsubstituted or substituted $C_5$-$C_{10}$aryl is, for example, phenyl, indenyl, indanyl, naphthyl, or 1,2,3,4-tetrahydronaphthalenyl, optionally substituted by $C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, hydroxy, $C_1$-$C_8$alkoxy, methylenedioxy, amino, substituted amino, halogen, carboxy, $C_1$-$C_8$alkoxycarbonyl, carbamoyl, sulfamoyl, cyano or nitro; preferably phenyl, tolyl, trifluoromethylphenyl, methoxyphenyl, dimethoxyphenyl, methylenedioxyphenyl, chlorophenyl or bromophenyl, whereby the substituents may be in ortho, meta or para position, preferably meta or para.

$C_5$-$C_{10}$aryloxy is especially phenoxy or methoxyphenoxy, e.g. p-methoxyphenoxy.

$C_5$-$C_{10}$aryl$C_1$-$C_8$alkyl is especially benzyl or 2-phenylethyl.

$C_5$-$C_{10}$aryl$C_1$-$C_8$alkoxy is especially benzyloxy or 2-phenylethoxy.

Unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1, 2 or 3 hetero atoms selected from N, O and S may be unsaturated, partially unsaturated or saturated, and further condensed to a benzo group or a 5 or 6 membered heterocyclyl group, and may be bound through a hetero or a carbon atom, and is, for example, pyrrolyl, indolyl, pyrrolidinyl, imidazolyl, benzimidazolyl, pyrazolyl, triazolyl, benzotriazolyl, tetrazolyl, pyridyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, piperidyl, pyrimidinyl, pyrazinyl, piperazinyl, purinyl, tetrazinyl, oxazolyl, isoxalyl, morpholinyl, thiazolyl, benzothiazolyl, oxadiazolyl, and benzoxadiazolyl. Substituents considered are $C_1$-$C_8$alkyl, hydroxy$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy$C_1$-$C_8$alkoxy, halo$C_1$-$C_8$alkyl, hydroxy, amino, substituted amino, $C_1$-$C_8$alkoxy, halogen, carboxy, $C_1$-$C_8$alkylcarbonyl, $C_0$-$C_8$alkoxycarbonyl, carbamoyl, $C_1$-$C_8$alkylcarbamoyl, cyano, oxo, or unsubstituted or substituted 5 or 6 membered heterocyclyl as defined in this paragraph. 5 or 6 membered heterocyclyl preferably comprises 1 or 2 hetero atoms selected from N, O and S, and is especially indolyl, pyrrolidinyl, pyrrolidonyl, imidazolyl, N-methylimidazolyl, benzimidazolyl, S,S-dioxoisothiazolidinyl, piperidyl, 4-acetylaminopiperidyl, 4-methylcarbamoylpiperidyl, 4-piperidinopiperidyl, 4-cyanopiperidyl, piperazinyl, N-methylpiperazinyl, N-(2-hydroxyethyl)piperazinyl, morpholinyl, 1-aza-2,2-dioxo-2-thiacyclohexyl, or sulfolanyl.

In unsubstituted or substituted heterocyclyloxy, heterocyclyl has the meaning as defined above, and is especially N-methyl-4-piperidyloxy. In unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, heterocyclyl has the meaning as defined above, and is especially 2-pyrrolidinoethoxy, 2-morpholinoethoxy, 3-morpholinopropoxy, 1-methyl-piperidin-3-ylmethoxy, 3-(N-methylpiperazino)propoxy or 2-(1-imidazolyl)ethoxy.

In a 5 or 6 membered carbocyclic or heterocyclic ring comprising 0, 1, 2 or 3 heteroatoms selected from N, O and S, and formed by two adjacent substituents together with the benzene ring, the ring may be further substituted, e.g. by $C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy, halo$C_1$-$C_8$alkyl, hydroxy, amino, substituted amino, $C_1$-$C_8$alkoxy, halogen, carboxy, $C_1$-$C_8$alkoxycarbonyl, carbamoyl, cyano, or oxo. The two adjacent substituents forming such a ring are preferably propylene, butylene, 1-aza-2-propylidene, 3-aza-1-propylidene, 1,2-diaza-2-propylidene, 2,3-diaza-1-propylidene, 1-oxapropylene, 1-oxapropylidene, methylenedioxy, difluoromethylenedioxy, 2-aza-1-oxopropylene, 2-aza-2-methyl-1-oxopropylene, 1-aza-2-oxopropylene, 2-aza-1,1-dioxo-1-thiapropylene or the corresponding butylene derivatives forming a 6 membered ring.

Salts are especially the pharmaceutically acceptable salts of compounds of formula I.

Such salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalenedisulfonic acid, 2-, 3- or 4-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

In view of the close relationship between the novel compounds in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the free compounds hereinbefore and hereinafter is to be understood as referring also to the corresponding salts, as appropriate and expedient.

The compounds of formula I have valuable pharmacological properties, as described hereinbefore and hereinafter.

In formula I the following significances are preferred independently, collectively or in any combination or sub-combination. In each of the following significances A is C or N preferably C:

(a) each of $R^0$ or $R^2$ independently is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl, ethyl or isopropyl, hydroxy$C_1$-$C_8$alkyl, e.g. hydroxyethyl or hydroxybutyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, $C_1$-$C_8$alkoxy, e.g. methoxy, ethoxy or isopropoxy, halo$C_1$-$C_8$alkoxy, e.g. trifluoromethoxy, $C_5$-$C_{10}$aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-Imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, $C_1$-$C_8$alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy, in particular hydrogen;

(b) $R^1$ is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl, ethyl or isopropyl, hydroxy$C_1$-$C_8$alkyl, e.g. hydroxyethyl or hydroxybutyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, $C_1$-$C_8$alkoxy, e.g. methoxy, ethoxy or isopropoxy, halo$C_1$-$C_8$alkoxy, e.g. trifluoromethoxy, $C_5$-$C_{10}$aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, $C_1$-$C_8$alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy, in particular hydrogen;

(c) $R^3$ is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl or ethyl, hydroxy$C_1$-$C_8$alkyl, e.g. hydroxyethyl or hydroxybutyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, e.g. 2-pyrrolidonyl or S,S-dioxoisothiazolidinyl, $C_1$-$C_8$alkoxy, e.g. methoxy, substituted amino, e.g. acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, $C_1$-$C_8$alkylsulfonyl, e.g. methylsulfonyl, $C_5$-$C_{10}$arylsulfonyl, e.g. phenylsulfonyl, halogen, e.g. fluoro or chloro, carboxy, substituted or unsubstituted carbamoyl, e.g. carbamoyl, methylcarbamoyl or dimethylcarbamoyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, isobutylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylsulfamoyl or morpholinosulfonyl; preferably sulfamoyl, methylsulfamoyl or propylsulfamoyl;

(d) each pair of adjacent substituents $R^0$ and $R^1$, or $R^1$ and $R^2$, or $R^2$ and $R^3$ are —$CH_2$—NH—O—, —$CH_2$—$CH_2$—NH—CO—, —$CH_2$—CO—NH—, —$CH_2$—$CH_2$—CO—NH—, —$CH_2$—NH—$SO_2$—, —$CH_2$—$CH_2$—NH—$SO_2$—, —$CH_2$—$SO_2$—NH—, —$CH_2$—$CH_2SO_2$—NH—, —$CH_2$—$CH_2$—$SO_2$—, —$CH_2$—$CH_2$—$CH_2$—$SO_2$—, —O—$CH_2$—O—, or —O—$CF_2$—O—, and such pairs wherein hydrogen in NH is replaced by $C_1$-$C_8$alkyl; preferably the pair of adjacent substituents $R^0$ and $R^1$, or $R^1$ and $R^2$ being —O—$CH_2$—O—, and the pair of adjacent substituents $R^2$ and $R^3$ being —$CH_2$—NH—CO— or —$CH_2$—NH—$SO_2$—.

(e) $R^4$ is hydrogen or $C_1$-$C_8$alkyl, e.g. methyl; preferably hydrogen;

(f) $R^5$ is hydrogen; $C_1$-$C_8$alkyl, e.g. methyl or ethyl, halogen, e.g. chloro or bromo, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, cyano or nitro; preferably hydrogen, methyl, ethyl, chloro, bromo, trifluoromethyl or nitro; in particular chloro or bromo;

(g) $R^6$ is hydrogen;

(h) each of $R^7$ and $R^9$ independently is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl, ethyl or isopropyl, hydroxy$C_1$-$C_8$alkyl, e.g. hydroxyethyl or hydroxybutyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, $C_1$-$C_8$alkoxy, e.g. methoxy, ethoxy or isopropoxy, halo$C_1$-$C_8$alkoxy, e.g. trifluoromethoxy, $C_5$-$C_{10}$aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, $C_1$-$C_8$alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

(i) $R^8$ is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl, ethyl or isopropyl, hydroxy$C_1$-$C_8$alkyl, e.g. hydroxyethyl or hydroxybutyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, $C_5$-$C_{10}$aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, $C_1$-$C_8$alkoxy, e.g. methoxy, ethoxy or isopropoxy, halo$C_1$-$C_8$alkoxy, e.g. trifluoromethoxy, $C_5$-$C_{10}$aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, $C_1$-$C_8$alkylsulfonyl, e.g. methylsulfonyl, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl, cyano, or nitro; preferably hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro;

(j) $R^{10}$ is $C_1$-$C_8$alkyl, e.g. methyl, ethyl or butyl, hydroxy$C_1$-$C_8$alkyl, e.g. hydroxyethyl or hydroxybutyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, $C_1$-$C_8$alkoxy, e.g. methoxy or ethoxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro; carboxy, carbamoyl, or unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; and

(k) each pair of adjacent substituents $R^7$ and $R^8$, or $R^8$ and $R^9$ or $R^9$ and $R^{10}$, are —NH—CH=CH—, —CH=CH—NH—, —NH—N=CH—, —CH=N—NH—, —$CH_2$—$CH_2$—$CH_2$—, —$CH_2$—$CH_2$—$CH_2$—$CH_2$—, —$CH_2$—$CH_2$—O—, —CH=CH—O—, —O—$CH_2$—O—, or —O—$CF_2$—O—; preferably the pair of adjacent substituents $R^7$ and $R^8$ or $R^8$ and $R^9$ being —O—$CH_2$—O— or the pair of adjacent substituents $R^9$ and $R^{10}$ being —NH—CH=CH—, —CH=N—NH—, —$CH_2$—$CH_2$—$CH_2$—, —$CH_2$—$CH_2$—$CH_2$—$CH_2$— or —O—$CF_2$—O—.

More preferred are the following meanings, independently, collectively or in any combination or sub-combination:

(a') each of $R^0$ or $R^2$ independently is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl, ethyl or isopropyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, $C_1$-$C_8$alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro; preferably hydrogen, piperazino, N-methylpiperazino or 1-methyl-4-piperidyloxy, in particular hydrogen;

(b') $R^1$ is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl, ethyl or isopropyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, $C_1$-$C_8$alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro; preferably hydrogen, piperazino, N-methylpiperazino, morpholino, 1-methyl-4-piperidinyloxy, 3-morpholinopropoxy or 2-morpholinoethoxy, in particular hydrogen;

(c') $R^3$ is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl or ethyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 heteroatoms selected from N, O and S, e.g. 2-pyrrolidonyl or S,S-dioxoisothiazolidinyl, $C_1$-$C_8$alkoxy, e.g. methoxy, substituted amino, e.g. acetylamino, acetyl-methyl-amino, benzoylamino, methylsulfonylamino or phenylsulfonylamino, $C_1$-$C_8$alkylsulfonyl, e.g. methylsulfonyl, $C_5$-$C_{10}$arylsulfonyl, e.g. phenylsulfonyl, halogen, e.g. fluoro or chloro, carboxy, substituted or unsubstituted carbamoyl, e.g. carbamoyl, methylcarbamoyl or dimethylcarbamoyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl, propylsulfamoyl, isopropylsulfamoyl, isobutylsulfamoyl, cyclopropylmethyl-sulfamoyl, 2,2,2-trifluoroethylsulfamoyl, dimethylsulfamoyl or morpholinosulfonyl; preferably sulfamoyl, methylsulfamoyl or propylsulfamoyl;

(d') each pair of adjacent substituents $R^0$ and $R^1$, or $R^1$ and $R^2$, or $R^2$ and $R^3$ are —$CH_2$—NH—CO—, —$CH_2$—NH—$SO_2$—, —$CH_2CH_2$—$SO_2$—, —O—$CH_2$—O—, or —O—$CF_2$—O—, and such pairs wherein hydrogen in NH is replaced by $C_1$-$C_8$alkyl; preferably the pair of adjacent substituents $R^0$ and $R^1$, or $R^1$ and $R^2$ being —O—$CH_2$—O—, and the pair of adjacent substituents $R^2$ and $R^3$ being —$CH_2$—NH—CO— or —$CH_2$—NH—$SO_2$—.

(e') $R^4$ is hydrogen;

(f) $R^5$ is hydrogen, halogen, e.g. chloro or bromo, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, or nitro; preferably hydrogen, chloro, bromo, trifluoromethyl or nitro; in particular chloro or bromo;

(g') $R^6$ is hydrogen;

(h') each of $R^7$ and $R^9$ independently is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl, ethyl or isopropyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, $C_1$-$C_8$alkoxy, e.g. methoxy, ethoxy or isopropoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino, dimethylamino or acetylamino, halogen, e.g. fluoro or chloro, unsubstituted or substituted carbamoyl, e.g. cyclohexylcarbamoyl, piperidinocarbonyl, piperazinocarbonyl, N-methylpiperazinocarbonyl or morpholinocarbonyl, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl; preferably hydrogen, methyl, isopropyl, trifluoromethyl, phenyl, o-, m- or p-methoxyphenyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, isopropoxy, phenoxy, 3 morpholinopropoxy, 2-morpholinoethoxy, 2-(1-imidazolyl)ethoxy, dimethylamino, fluoro, morpholinocarbonyl, piperidinocarbonyl, piperazinocarbonyl or cyclohexylcarbamoyl;

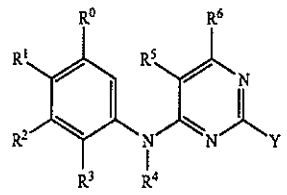
(i') $R^8$ is hydrogen, $C_1$-$C_8$alkyl, e.g. methyl, ethyl or isopropyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, $C_5$-$C_{10}$aryl, e.g. phenyl or methoxyphenyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, e.g. morpholino, piperidino, piperazino or N-methylpiperazino, $C_1$-$C_8$alkoxy, e.g. methoxy, ethoxy or isopropoxy, halo$C_1$-$C_8$alkoxy, e.g. trifluoromethoxy, $C_5$-$C_{10}$aryloxy, e.g. phenoxy, unsubstituted or substituted heterocyclyloxy, e.g. 1-methyl-4-piperidyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, 3-morpholinopropoxy or 2-morpholinoethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro, unsubstituted or substituted sulfamoyl, e.g. sulfamoyl, methylsulfamoyl or dimethylsulfamoyl, or nitro; preferably hydrogen, methyl, piperidino, piperazino, N-methylpiperazino, morpholino, methoxy, ethoxy, trifluoromethoxy, phenoxy, 1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy, 3-(N-methylpiperazino)-propoxy, methylamino, fluoro, chloro, sulfamoyl or nitro;

(j') $R^{10}$ is $C_1$-$C_8$alkyl, e.g. methyl, ethyl or butyl, halo$C_1$-$C_8$alkyl, e.g. trifluoromethyl, $C_1$-$C_8$alkoxy, e.g. methoxy or ethoxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, e.g. 2-(1-imidazolyl)ethoxy, unsubstituted or substituted amino, e.g. methylamino or dimethylamino, halogen, e.g. fluoro or chloro; preferably methyl, butyl, methoxy, ethoxy, 2-(1-imidazolyl)ethoxy, methylamino, dimethylamino or fluoro; and

(k') each pair of adjacent substituents $R^7$ and $R^8$, or $R^8$ and $R^9$ or $R^9$ and $R^{10}$, are —NH—CH=CH—, —CH=CH—NH—, —NH—N=CH—, —CH=N—NH—, —$CH_2$—$CH_2$—$CH_2$—, —$CH_2$—$CH_2$—$CH_2CH_2$—, —O—$CH_2$—O—, or —O—$CF_2$—O—; preferably the pair of adjacent substituents $R^7$ and $R^8$ or $R^8$ and $R^9$ being —O—$CH_2$—O— or the pair of adjacent substituents $R^9$ and $R^{10}$ being —NH—CH=CH—, —CH=N—NH—, —$CH_2$—$CH_2$—$CH_2$—, —$CH_2$—$CH_2$—$CH_2$—$CH_2$— or —O—$CF_2$—O—.

Most preferred as compounds of the formula I are those wherein the substituents have the meaning given in the Examples.

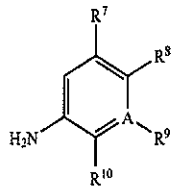
The present invention also provides a process for the production of a compound of formula I, comprising reacting a compound of formula II



(II)

wherein $R^0$, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, and $R^6$ are as defined above, and Y is a leaving group, preferably halogen such as bromide, iodine, or in particular chloride;

with a compound of formula III



(III)

wherein $R^7$, $R^8$, $R^9$ and $R^{10}$ are as defined above;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined above, into another compound of formula I as defined;

and recovering the resulting compound of formula I in free from or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

The reaction can be carried out in a manner known per se, the reaction conditions being dependent especially on the reactivity of the leaving group Y and the reactivity of the amino group in the aniline of formula III, usually in the presence of a suitable solvent or diluent or of a mixture thereof and, if necessary, in the presence of an acid or a base, with cooling or, preferably, with heating, for example in a temperature range from approximately −30° C. to approximately +150° C., especially approximately from 0° C. to +100° C., preferably from room temperature (approx. +20° C.) to +80° C., in an open or closed reaction vessel and/or in the atmosphere of an inert gas, for example nitrogen.

If one or more other functional groups, for example carboxy, hydroxy or amino, are or need to be protected in a compound of formula II or III, because they should not take part in the reaction, these are such groups as are usually used in the synthesis of peptide compounds, cephalosporins and penicillins, as well as nucleic acid derivatives and sugars.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as substitution reaction or solvolysis. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known per se. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent.

Salts can usually be converted to compounds in free form, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known per se by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of dias-

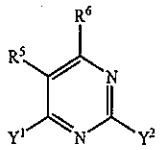
tereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands.

It should be emphasized that reactions analogous to the conversions mentioned in this chapter may also take place at the level of appropriate intermediates.

The compounds of formula I, including their salts, are also obtainable in the form of hydrates, or their crystals can include for example the solvent used for crystallization (present as solvates).

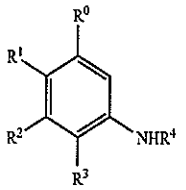
The compound of formula II used as starting materials may be obtained by reacting a compound of formula IV

(IV)



with a compound of formula V

(V)



wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$ and $R^6$ are as defined above, and $Y^1$ and $Y^2$ are identical or different leaving groups as defined above for Y. The reaction conditions are those mentioned above for the reaction of a compound of formula II with a compound of formula III.

The compounds of formula IV and V are known or may be produced in accordance with known procedures.

The compounds of formula I and their pharmaceutically acceptable salts exhibit valuable pharmacological properties when tested in vitro in cell-free kinase assays and in cellular assays, and are therefore useful as pharmaceuticals. In particular, the compounds of the invention are inhibitors of Focal Adhesion Kinase, and are useful as pharmaceuticals to treat conditions caused by a malfunction of signal cascades connected with Focal Adhesion Kinase, in particular tumors as described hereinbelow.

Focal Adhesion Kinase (FAK) is a key enzyme in the integrin-mediated outside-in signal cascade (D. Schlaepfer et al., Prog Biophys Mol Biol 1999, 71, 435-478). Interaction between cells and extracellular matrix (ECM) proteins is transduced as intracellular signals important for growth, survival and migration through cell surface receptors, integrins. FAK plays an essential role in these integrin-mediated outside-in signal cascades. The trigger in the signal transduction cascade is the autophosphorylation of Y397. Phosphorylated Y397 is a SH2 docking site for Src family tyrosine kinases. The bound c-Src kinase phosphorylates other tyrosine residues in FAK. Among them, phsophorylated Y925 becomes a binding site for the SH2 site of Grb2 small adaptor protein. This direct binding of Grb2 to FAK is one of the key steps for the activation of down stream targets such as the Ras-ERK2/MAP kinase cascade.

The inhibition of endogenous FAK signalling results in reduced motility and in some cases induces cell death. On the other hand, enhancing FAK signalling by exogenous expression increases cell motility and transmitting a cell survival signal from ECM. In addition FAK is overexpressed in invasive and metastatic epithelial, mesenchymal, thyroid and prostate cancers. Consequently, an inhibitor of FAK is likely to be a drug for anti-tumor growth and metastasis. The compounds of the invention are thus indicated, for example, to prevent and/or treat a vertebrate and more particularly a mammal, affected by a neoplastic disease, in particular breast tumor, cancer of the bowel (colon and rectum), stomach cancer and cancer of the ovary and prostate, non-small cell lung cancer, small cell lung cancer, cancer of liver, melanoma, bladder tumor and cancer of head and neck.

The relation between FAK inhibition and immuno-system is described e.g. in G. A. van Seventer et al., Eur. J. Immunol. 2001, 31, 1417-1427. Therefore, the compounds of the invention are, for example, useful to prevent and/or treat a vertebrate and more particularly a mammal, affected by immune system disorders, diseases or disorders mediated by T lymphocytes, B lymphocytes, mast cells and/or eosinophils e.g. acute or chronic rejection of organ or tissue allo- or xenografts, atherosclerosis, vascular occlusion due to vascular injury such as angioplasty, restenosis, hypertension, heart failure, chronic obstructive pulmonary disease, CNS disease such as Alzheimer disease or amyotrophic lateral sclerosis, cancer, infectious disease such as AIDS, septic shock or adult respiratory distress syndrome, ischemia/reperfusion injury e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, or traumatic shock. The agent of the invention are also useful in the treatment and/or prevention of acute or chronic inflammatory diseases or disorders or autoimmune diseases e.g. rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, diabetes (type I and II) and the disorders associated with therewith, respiratory diseases such as asthma or inflammatory liver injury, inflammatory glomerular injury, cutaneous manifestations of immunologically-mediated disorders or illnesses, inflammatory and hyperproliferative skin diseases (such as psoriasis, atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis), inflammatory eye diseases, e.g. Sjoegren's syndrome, keratoconjunctivitis or uveitis, inflammatory bowel disease, Crohn's disease or ulcerative colitis.

Compounds of the invention are active in a FAK assay system as described in the Examples, and show an inhibition $IC_{50}$ in the range of 1 nM to 100 nM. Particularly active are the compounds Example No. 3-12 and No. 3-17 described hereinbelow showing $IC_{50}$ vales in the range of 1 to 5 nM.

Some of the compounds of the invention exhibit also ZAP-70 (zeta chain-associated protein of 70 kD) protein tyrosine kinase inhibiting activity. ZAP-70 protein tyrosine kinase interaction of the agents of the invention may be demonstrated by their ability to prevent phosphorylation of e.g. LAT-11 (linker for activation of T cell) by human ZAP-70 protein tyrosine kinase in aqueous solution, as described in the Examples. The compounds of the invention are thus also indicated for the prevention or treatment of disorders or diseases where ZAP-70 inhibition inhibition play a role.

Compounds of the invention are active in a ZAP-70 assay system as described in the Examples, and show an inhibition $IC_{50}$ in the range of 1 μM to 10 μM, e.g. the compounds Example No. 2 and No. 3-2 described hereinbelow.

Compounds of the present invention are also good inhibitors of the IGF-IR (insulin like growth factor receptor 1) and

are therefore useful in the treatment of IGF-1R mediated diseases for example such diseases include proliferative diseases, such as tumours, like for example breast, renal, prostate, colorectal, thyroid, ovarian, pancreas, neuronal, lung, uterine and gastrointestinal tumours as well as osteosarcomas and melanomas. The efficacy of the compounds of the invention as inhibitors of IGF-IR tyrosine kinase activity can be demonstrated using a cellular "Capture ELISA". In this assay the activity of the compounds of the invention against Insulin-like growth factor I (IGF-I) induced autophosphorylation of the IGF-IR is determined.

The compounds of the present invention also exhibit powerful inhibition of the tyrosine kinase activity of anaplastic lymphoma kinase (ALK) and the fusion protein of NPM-ALK. This protein tyrosine kinase results from a gene fusion of nucleophosmin (NPM) and the anaplastic lymphoma kinase (ALK), rendering the protein tyrosine kinase activity of ALK ligand-independent. NPM-ALK plays a key role in signal transmission in a number of hematopoetic and other human cells leading to hematological and neoplastic diseases, for example in anaplastic large-cell lymphoma (ALCL) and non-Hodgkin's lymphomas (NHL), specifically in ALK+NHL or Alkomas, in inflammatory myofibroblastic tumors (IMT) and neuroblastomas. (Duyster J et al. 2001 Oncogene 20, 5623-5637). In addition to NPM-ALK, other gene fusions have been identified in human hematological and neoplastic diseases; mainly TPM3-ALK (a fusion of nonmuscle tropomyosin with ALK).

The inhibition of ALK tyrosine kinase activity can be demonstrated using known methods, for example using the recombinant kinase domain of the ALK in analogy to the VEGF-R kinase assay described in J. Wood et al. Cancer Res. 60, 2178-2189 (2000). In vitro enzyme assays using GST-ALK protein tyrosine kinase are performed in 96-well plates as a filter binding assay in 20 mM Tris.HCl, pH=7.5, 3 mM $MgCl_2$, 10 mM $MnCl_2$, 1 mM DTT, 0.1 μCi/assay (=30 μl) [$\gamma$-$^{33}$P]-ATP, 2 μM ATP, 3 μg/ml poly (Glu, Tyr 4:1) Poly-EY (Sigma P-0275), 1% DMSO, 25 ng ALK enzyme. Assays are incubated for 10 min at ambient temperature. Reactions are terminated by adding 50 μl of 125 mM EDTA, and the reaction mixture is transferred onto a MAIP Multiscreen plate (Millipore, Bedford, Mass., USA), previously wet with methanol, and rehydrated for 5 min with $H_2O$. Following washing (0.5% $H_3PO_4$), plates are counted in a liquid scintillation counter. $IC_{50}$ values are calculated by linear regression analysis of the percentage inhibition. Compared with the control without inhibitor, the compounds of formula I inhibit the enzyme activity by 50% ($IC_{50}$), for example in a concentration of from 0.001 to 0.5 μM, especially from 0.01 to 0.1 μM.

The compounds of formula I potently inhibit the growth of human NPM-ALK overexpressing murine BaF3 cells (DSMZ Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig, Germany). The expression of NPM-ALK is achieved by transfecting the BaF3 cell line with an expression vector pCIneo™ (Promega Corp., Madison Wis., USA) coding for NPM-ALK and subsequent selection of G418 resistant cells. Non-transfected BaF3 cells depend on IL-3 for cell survival. In contrast NPM-ALK expressing BaF3 cells (named BaF3-NPM-ALK hereinafter) can proliferate in the absence of IL-3 because they obtain proliferative signal through NPM-ALK kinase. Putative inhibitors of the NPM-ALK kinase therefore abolish the growth signal and result in antiproliferative activity. The antiproliferative activity of putative inhibitors of the NPM-ALK kinase can however be overcome by addition of IL-3 which provides growth signals through an NPM-ALK independent mechanism. [For an analogous cell system using FLT3 kinase see E Weisberg et al. Cancer Cell; 1, 433-443 (2002)]. The inhibitory activity of the compounds of formula I is determined, briefly, as follows: BaF3-NPM-ALK cells (15,000/microtitre plate well) are transferred to 96-well microtitre plates. The test compounds [dissolved in dimethyl sulfoxide (DMSO)] are added in a series of concentrations (dilution series) in such a manner that the final concentration of DMSO is not greater than 1% (v/v). After the addition, the plates are incubated for two days during which the control cultures without test compound are able to undergo two cell-division cycles. The growth of the BaF3-NPM-ALK cells is measured by means of Yopro™ staining [T Idziorek et al. J. Immunol. Methods; 185: 249-258 (1995)]: 25 μl of lysis buffer consisting of 20 mM sodium citrate, pH 4.0, 26.8 mM sodium chloride, 0.4% NP40, 20 mM EDTA and 20 mM is added to each well. Cell lysis is completed within 60 min at room temperature and total amount of Yopro bound to DNA is determined by measurement using the Cytofluor II 96-well reader (PerSeptive Biosystems) with the following settings: Excitation (nm) 485/20 and Emission (nm) 530/25.

$IC_{50}$ values are determined by a computer-aided system using the formula:

$$IC_{50}=[(ABS_{test}-ABS_{start})/(ABS_{control}-ABS_{start})]\times 100.$$

(ABS=absorption)

The $IC_{50}$ value in those experiments is given as that concentration of the test compound in question that results in a cell count that is 50% lower than that obtained using the control without inhibitor. The compounds of formula I exhibit inhibitory activity with an $IC_{50}$ in the range from approximately 0.01 to 1 μM.

The antiproliferative action of the compounds of formula I can also be determined in the human KARPAS-299 lymphoma cell line (DSMZ Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Braunschweig, Germany) [described in W G Dirks et al. Int. J. Cancer 100, 49-56 (2002)] using the same methodology described above for the BaF3-NPM-ALK cell line. The compounds of formula I exhibit inhibitory activity with an $IC_{50}$ in the range from approximately 0.01 to 1 μM.

The action of the compounds of formula I on autophosphorylation of the ALK can be determined in the human KARPAS-299 lymphoma cell line by means of an immunoblot as described in W G Dirks et al. Int. J. Cancer 100, 49-56 (2002). In that test the compounds of formula I exhibit an $IC_{50}$ of approximately from 0.001 to 1 μM.

Among the compounds of formula I, 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide is an especially potent ALK inhibitor, in that this compound inhibits the growth of the BaF3-NPM-ALK cells with an $IC_{50}$ of 97 nM. Further specifically preferred compounds that inhibit the tyrosine kinase activity of anaplastic lymphoma kinase (ALK) are the compounds described hereinafter in the examples 7A and 7B, as well as 7-2, 7-15, 7-36, 7-39, 7-44 and 7-52, respectively, all of which are having an $IC_{50}$ within the range from <0.5 to 200 nM.

For the above uses in the treatment of neoplastic diseases and immune system disorders the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.1 to about 100 mg/kg body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to

about 2000 mg, conveniently administered, for example, in divided doses up to four times a day or in retard form.

The compounds of the invention may be administered by any conventional route, in particular parenterally, for example in the form of injectable solutions or suspensions, enterally, preferably orally, for example in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent. Unit dosage forms for oral administration contain, for example, from about 0.1 mg to about 500 mg of active substance. Topical administration is e.g. to the skin. A further form of topical administration is to the eye.

The pharmaceutical compositions of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, dissolving or lyophilizing processes.

Preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions, especially isotonic aqueous solutions, dispersions or suspensions which, for example in the case of lyophilized compositions comprising the active ingredient alone or together with a carrier, for example mannitol, can be made up before use. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers and are prepared in a manner known per se, for example by means of conventional dissolving and lyophilizing processes. The said solutions or suspensions may comprise viscosity-increasing agents, typically sodium carboxymethylcellulose, carboxymethylcellulose, dextran, polyvinylpyrrolidone, or gelatins, or also solubilizers, e.g. Tween 80® (polyoxyethylene(20)sorbitan mono-oleate).

Suspensions in oil comprise as the oil component the vegetable, synthetic, or semisynthetic oils customary for injection purposes. In respect of such, special mention may be made of liquid fatty acid esters that contain as the acid component a long-chained fatty acid having from 8 to 22, especially from 12 to 22, carbon atoms, for example lauric acid, tridecylic acid, myristic acid, pentadecylic acid, palmitic acid, margaric acid, stearic acid, arachidic acid, behenic acid or corresponding unsaturated acids, for example oleic acid, elaidic acid, erucic acid, brassidic acid or linoleic acid, if desired with the addition of antioxidants, for example vitamin E, β-carotene or 3,5-di-tert-butyl-4-hydroxytoluene. The alcohol component of these fatty acid esters has a maximum of 6 carbon atoms and is a monovalent or polyvalent, for example a mono-, di- or trivalent, alcohol, for example methanol, ethanol, propanol, butanol or pentanol or the isomers thereof, but especially glycol and glycerol. As fatty acid esters, therefore, the following are mentioned: ethyl oleate, isopropyl myristate, isopropyl palmitate, "Labrafil M 2375" (polyoxyethylene glycerol), "Labrafil M 1944 CS" (unsaturated polyglycolized glycerides prepared by alcoholysis of apricot kernel oil and consisting of glycerides and polyethylene glycol ester), "Labrasol" (saturated polyglycolized glycerides prepared by alcoholysis of TCM and consisting of glycerides and polyethylene glycol ester; all available from Gattefossé, France), and/or "Miglyol 812" (triglyceride of saturated fatty acids of chain length $C_8$ to $C_{12}$ from Hüls AG, Germany), but especially vegetable oils such as cottonseed oil, almond oil, olive oil, castor oil, sesame oil, soybean oil and more especially groundnut oil.

The manufacture of injectable preparations is usually carried out under sterile conditions, as is the filling, for example, into ampoules or vials, and the sealing of the containers.

Pharmaceutical compositions for oral administration can be obtained, for example, by combining the active ingredient with one or more solid carriers, if desired granulating a resulting mixture, and processing the mixture or granules, if desired or necessary, by the inclusion of additional excipients, to form tablets or tablet cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations, and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example corn, wheat, rice or potato starch, methylcellulose, hydroxypropyl methylcellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone, and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, alginic acid or a salt thereof, such as sodium alginate. Additional excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol, or derivatives thereof.

Tablet cores can be provided with suitable, optionally enteric, coatings through the use of, inter alia, concentrated sugar solutions which may comprise gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or tablet coatings, for example for identification purposes or to indicate different doses of active ingredient.

Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer, such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as corn starch, binders, and/or glidants, such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, such as fatty oils, paraffin oil or liquid polyethylene glycols or fatty acid esters of ethylene or propylene glycol, to which stabilizers and detergents, for example of the polyoxyethylene sorbitan fatty acid ester type, may also be added.

Pharmaceutical compositions suitable for rectal administration are, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

For parenteral administration, aqueous solutions of an active ingredient in water-soluble form, for example of a water-soluble salt, or aqueous injection suspensions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, if desired, stabilizers, are especially suitable. The active ingredient, optionally together with excipients, can also be in the form of a lyophilizate and can be made into a solution before parenteral administration by the addition of suitable solvents.

Solutions such as are used, for example, for parenteral administration can also be employed as infusion solutions.

Preferred preservatives are, for example, antioxidants, such as ascorbic acid, or microbicides, such as sorbic acid or benzoic acid.

The compounds of the invention may be administered as the sole active ingredient or together with other drugs useful against neoplastic diseases or useful in immunomodulating regimens. For example, the agents of the invention may be used in accordance with the invention in combination with pharmaceutical compositions effective in various diseases as described above, e.g. with cyclophosphamide, 5-fluorouracil, fludarabine, gemcitabine, cisplatinum, carboplatin, vincristine, vinblastine, etoposide, irinotecan, paclitaxel, docetaxel, rituxan, doxorubicine, gefitinib, or imatinib; or also with cyclosporins, rapamycins, ascomycins or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, sirolimus or everolimus, corticosteroids, e.g. prednisone, cyclophosphamide, azathioprene, methotrexate, gold salts, sulfasalazine, antimalarials, brequinar, leflunomide, mizoribine, mycophenolic acid, mycophenolate, mofetil, 15-deoxyspergualine, immuno-suppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. MHC, CD2, CD3, CD4, CD7, CD25, CD28, CD40, CD45, CD58, CD80, CD86, CD152, CD137, CD154, ICOS, LFA-1, VLA-4 or their ligands, or other immunomodulatory compounds, e.g. CTLA4Ig.

In accordance with the foregoing, the present invention also provides:

(1) A compound of the invention for use as a pharmaceutical;

(2) a compound of the invention for use as a FAK inhibitor, an ALK inhibitor and/or ZAP-70 inhibitor, for example for use in any of the particular indications hereinbefore set forth;

(3) a pharmaceutical composition, e.g. for use in any of the indications herein before set forth, comprising a compound of the invention as active ingredient together with one or more pharmaceutically acceptable diluents or carriers;

(4) a method for the treatment of any particular indication set forth hereinbefore in a subject in need thereof which comprises administering an effective amount of a compound of the invention or a pharmaceutical composition comprising same;

(5) the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which FAK, ALK and/or ZAP-70 activation plays a role or is implicated;

(6) the method as defined above under (4) comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;

(7) a combination comprising a therapeutically effective amount of a compound of the invention and one or more further drug substances, said further drug substance being useful in any of the particular indications set forth hereinbefore;

(8) use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease which responds to inhibition of the anaplastic lymphoma kinase;

(9) the use according to (8), wherein the disease to be treated is selected from anaplastic large-cell lymphoma, non-Hodgkin's lymphomas, inflammatory myofibroblastic tumors and neuroblastomas;

(10) the use according to (8) or (9), wherein the compound is 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide or a pharmaceutically acceptable salt thereof, or any of the the compounds described hereinafter in the examples or a pharmaceutically acceptable salt of any one of these;

(11) a method for the treatment of a disease which responds to inhibition of the anaplastic lymphoma kinase, especially a disease selected from anaplastic large-cell lymphoma, non-Hodgkin's lymphomas, inflammatory myofibroblastic tumors and neuroblastomas, comprising administering an effective amount of a compound of the invention, especially 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide, or a pharmaceutically acceptable salt thereof.

Additionally preferred a compound according to the present invention that is useful as herein before described is a compound specifically mentioned in the examples.

Additional specifically preferred compounds according to the present invention that are useful either as FAK inhibitor, as ALK inhibitor or for inhibition of both and which may be prepared essentially according to the methods described hereinbefore are the following:

2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide,

$N^2$-(4-[1,4']Bipiperidinyl-1'-yl-2-methoxy-phenyl)-5-chloro-$N^4$-[2-(propane-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine,

2-{5-Chloro-2-[2-methoxy-4-(4-methyl-piperazin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-N-isopropyl-benzenesulfonamide,

2-[5-Bromo-2-(2-methoxy-5-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide

2-{2-[5-(1-Acetyl-piperidin-4-yloxy)-2-methoxy-phenylamino]-5-bromo-pyrimidin-4-ylamino}-N-methyl-benzenesulfonamide,

N-[5-Bromo-2-(2,5-dimethoxy-phenylamino)pyrimidin-4-yl]-N-(4-morpholin-4-yl-phenyl)-methanesulfonamide,

5-Bromo-N-4-(4-fluoro-phenyl)-N*2*-(2-methoxy-4-morpholin-4-yl-phenyl)pyrimidine-2,4-diamine,

2-[5-Chloro-2-(2-methoxy-4-piperazin-1-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide,

2-[5-Bromo-2-(5-fluoro-2-methoxy-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide,

2-[5-Chloro-2-(5-fluoro-2-methoxy-phenylamino)-pyrimidin-4-ylamino]-N-isobutyl-benzenesulfonamide, and

2-{5-Chloro-2-[2-methoxy-5-(4-methyl-piperazin-1-ylmethyl)-phenylamino]-pyrimidin-4-ylamino}-N-methyl-benzenesulfonamide.

The invention also provides a compound of formula 2-{5-Chloro-2-[4-(3-methylamino-pyrrolidin-1-yl)-phenylamino]-pyrimidin-4-ylamino}-N-isopropyl-benzenesulfonamide

The following Examples serve to illustrate the invention without limiting the invention in its scope.

## EXAMPLES

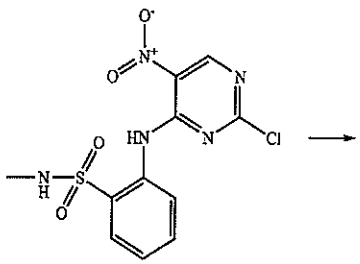
Abbreviations

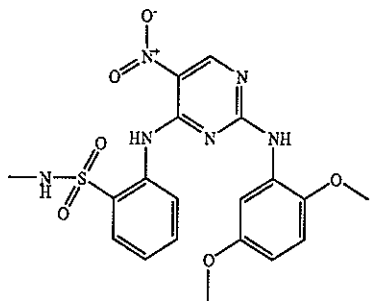
AcOH=acetic acid, ALK=anaplastic lymphoma kinase, ATP=adenosine 5'-triphosphate, brine=saturated sodium chloride solution, BSA=bovine serum albumin, DIAD=diisopropyl azodicarboxylate, DIPCDI=N,N'-diisopropylcarbodiimid, DMAP=4-dimethylaminopyridine, DMF=N,N-dimethylformamide, DTT=1,4-dithio-D,L-threitol, EDTA=ethylene diamine tetraacetic acid, Et=ethyl, EtOAc=ethyl acetate, EtOH=ethanol, Eu-PT66=LANCE™ europium-W1024-labelled anti-phosphotyrosine antibody (Perkin Elmer), FAK=Focal Adhesion Kinase, FRET=fluorescence resonance energy transfer, HEPES=N-2-hydroxyethyl-piperazine-N'-2-ethanesulfonic acid, HOAt=1-hydroxy-7-azabenzotriazole, Me=methyl,

RT-PCR=reverse transcription polymerase chain reaction, SA-(SL)APC=Streptavidin conjugated to SuperLight™ allophycocyanin (Perkin Elmer), subst.=substituted, TBTU=O-(benzotriazol-1-yl)-N,N,N',N'-tetramethylammonium tetrafluoroborate, THF=tetrahydrofuran.

Example 1

2-[2-(2,5-Dimethoxy-phenylamino)-5-nitro-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide





To a solution of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide (100 mg, 0.29 mmol) in EtOH (3 mL), 2,5-dimethoxyaniline (49 mg, 0.32 mmol) is added at room temperature. The mixture is heated at 78° C. for 5 h. The solvent is evaporated, and the mixture is purified by reverse phase HPLC to give the title product in.

Rf=0.47 (n-hexane:ethyl acetate=1:1). $^1$H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.36 (d, 3H), 3.57 (s, 3H), 3.73 (s, 3H), 6.72 (d, 1H), 6.99 (d, 1H), 7.17 (s, 1H), 7.35 (t, 1H), 7.4-7.6 (m, 1H), 7.63 (d, 1H), 7.81 (d, 1H), 8.0-8.2 (m, 1H), 9.13 (s, 1H), 9.41 (br.s, 1H), 11.0 (s, 1H).

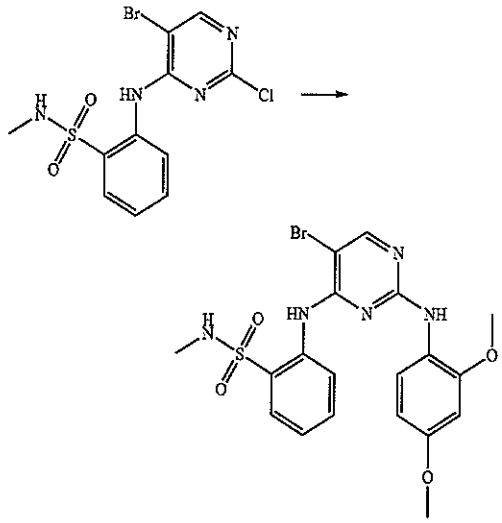
Preparation of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide

2,4-Dichloro-5-nitro-pyrimidine (1.94 g, 10 mmol) and 2-amino-N-methyl-benzenesulfonamide (1.86 g, 10 mmol) are dissolved in $CHCl_3$ (30 mL). The reaction mixture is heated at 61° C. for 2 h. The solvent is evaporated and the residue is washed with ether to give the title product.

Rf=0.5 (n-hexane:ethyl acetate=1:1). $^1$H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.6-4.7 (m, 2H), 7.41 (dd, 1H), 7.7 (dd, 1H), 8.04 (d, 1H), 8.15 (d, 1H), 9.21 (s, 1H), 11.2 (s, 1H).

Example 2

2-[5-Bromo-2-(2,4-dimethoxy-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide



To a solution of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide (300 mg, 0.79 mmol), 2,4-dimethoxyaniline (181.5 mg, 1.18 mmol) in ethanol (3 mL), 1 N hydrochloric acid (0.03 mL) is added and stirred under reflux condition for 5 hours. The reaction mixture is cooled to room temperature, poured into water and extracted twice with ethyl acetate. The organic layer is successively washed with water and brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane:ethyl acetate=5:1 to 1:1) to afford the title compound.

$^1$H-NMR ($CDCl_3$), δ (ppm): 8.95 (s, 1H), 8.44 (d, 1H), 8.20 (s, 1H), 7.98 (dd, 1H), 7.58 (ddd, 1H), 7.22-7.32 (m, 1H), 6.51 (d, 1H), 6.40 (d, 1H), 4.56-4.48 (m, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 2.64 (d, 3H). Rf (n-hexane:ethyl acetate=1:1): 0.31.

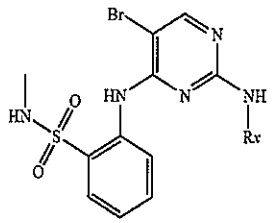
Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide

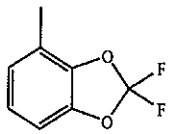
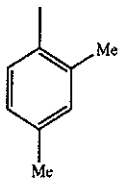
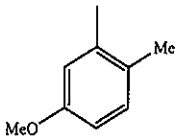
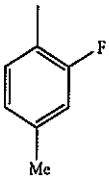
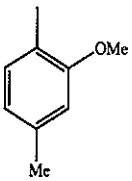
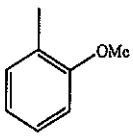
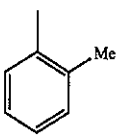
A solution of 5-bromo-2,4-dichloropyrimidine (684 mg, 3.0 mmol) and 2-amino-N-methyl-benzenesulfonamide (559 mg, 3.0 mmol) in N,N-dimethylformamide (10 mL) containing potassium carbonate (830 mg, 6.0 mmol) is stirred at room temperature for 23 hours. Saturated aqueous ammonium chloride is added and the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane-ethyl acetate gradient) to afford the title compound as a slightly yellow solid.

$^1$H-NMR ($CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.79 (q, 1H), 7.26 (s, 1H), 7.29 (ddd, 1H), 7.66 (ddd, 1H), 7.95 (dd, 1H), 8.37 (s, 1H), 8.48 (d, 1H), 9.52 (s, 1H). Rf (n-hexane:ethyl acetate=10:3): 0.33.

Example 3

The following 2-[5-bromo-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamides are prepared from 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 2:




| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-1 |  | 0.48 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.64(d, 3H), 4.48-4.40(m, 1H), 6.78(d, 1H), 6.87(bs, 1H), 6.99(dd, 1H), 6.82(8, 1H), 7.54(ddd, 1H), 7.79(d, 1H), 7.97(dd, 1H), 8.28(s, 1H), 8.32(dd, 1H), 9.07(s, 1H) |
| 3-2 |  | 0.58 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.25(s, 3H), 2.33(s, 3H), 2.63(d, 3H), 4.53-4.45(m, 1H), 6.61(bs, 1H), 6.99(dd, 1H), 7.04(s, 1H), 7.18(ddd, 1H), 7.43(ddd, 1H), 7.56(d, 1H), 7.92(dd, 1H), 8.19(s, 1H), 8.41(dd, 1H), 9.08(s, 1H) |
| 3-3 |  | 0.36 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.23(s, 3H), 2.62(d, 3H), 3.69(s, 3H), 4.53-4.44(m, 1H), 6.62(dd, 1H), 6.69(bs, 1H), 7.10(d, 1H), 7.19(dd, 1H), 7.48(d, 1H), 7.51(dd, 1H), 7.93(dd, 1H), 8.22(s, 1H), 8.44(dd, 1H), 9.09(s1, 1H) |
| 3-4 |  | 0.41 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.32(s, 3H), 2.63(d, 3H), 4.45-4.44(m, 1H), 6.85(d, 1H), 6.91(d, 1H), 7.00(bs, 1H), 7.28-7.24(m, 1H), 7.57(dd, 1H), 7.99(dd, 1H), 8.25(s, 1H), 8.39(d, 1H), 9.00(bs, 1H) |
| 3-5 |  | 0.39 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.33(s, 3H), 2.63(d, 3H), 3.87(s, 3H), 4.46-4.44(m, 1H), 6.66(d, 1H), 6.71(s, 1H), 7.48(bs, 1H), 7.63-7.59(m, 1H), 7.97(dd, 1H), 8.05(d, 1H), 8.23 (s, 1H), 8.44(d, 1H), 8.92(bs, 1H) |
| 3-6 |  | 0.27 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.63(d, 3H), 3.90(s, 3H), 4.45-4.40(m, 1H), 6.90–6.86(m, 2H), 7.00-6.96(m, 1H), 7.23–7.17 (m, 3H), 7.45(dd, 1H), 7.50-7.60(m, 2H), 7.97(dd, 1H), 8.22(d, 1H), 8.26 (S, 1H), 8.43(d, 1H), 8.94(bs, 1H) |
| 3-7 |  | 0.34 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.30(s, 3H), 2.63(d, 3H), 4.44-4.43(m, 1H), 6.68 (bs, 1H), 7.00-6.68(m, 1H), 7.23-7.17(m, 2H), 7.46–7.43(m, 1H), 7.76(d, 1H), 7.93(dd, 1H), 8.22 (s, 1H), 8.40(d, 1H), 9.01(bs, 1H) |

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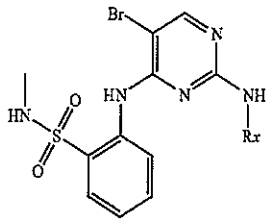
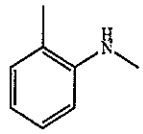
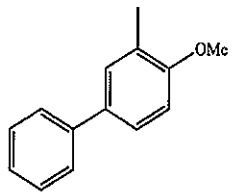
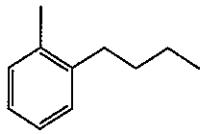
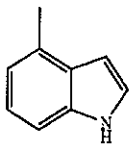
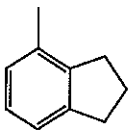
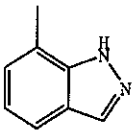
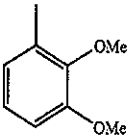
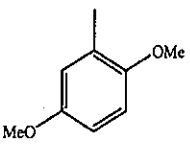


| ExpiNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-8 |  | 0.12 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.62(d, 3H), 2.81(s, 3H), 4.07-3.98(m, 1H), 4.52-4.45(m, 1H), 6.37(bs, 1H), 6.77-6.73 (m, 2H), 7.12(dd, 1H), 7.24-7.20(m, 1H), 7.30-7.27(m, 1H), 7.35(dd, 1H), 7.88(dd, 1H), 8.18 (S, 1H), 8.41(d, 1H), 9.19(bs, 1H) |
| 3-9 |  | 0.28 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.62(d, 3H), 3.94(s, 3H), 4.49–4.43(m, 1H), 6.99-6.90 (m, 3H), 7.18-7.23(m, 1H), 7.31-7.24(m, 3H), 7.63(bs, 1H), 7.93-7.86(m, 1H), 8.28-8.23(m, 1H), 8.28 (s, 1H), 8.45(bs, 1H), 8.89(bs, 1H) |
| 3-10 |  | 0.23 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 0.91(t, 3H), 1.37 (dd, 2H), 1.64-1.55(m, 2H), 2.64-2.60(m, 2H), 4.45-4.40(m, 1H), 6.69(bs, 1H), 7.23–7.10(m, 1H), 7.46-7.38(m, 1H), 7.73(d 1H), 7.92(d, 1H), 8.21(s, 1H), 8.38-8.46(m, 1H), 9.09(bs, 1H) |
| 3-11 |  | 0.12 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.63(d, 3H), 4.15-4.10(m, 1H), 6.58(bs, 1H), 7.31-7.10(m, 4H), 7.53-7.49(m, 1H), 7.71(d 1H), 7.95 (d, 1H), 8.30–8.23(m, 1H), 8.26(s, 1H), 8.45(d, 1H), 9.03(bs, 1H) |
| 3-12 |  | 0.4 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.09 (dd, 2H), 2.63 (d, 3H), 2.85(t, 2H), 2.96 (t, 2H), 4.46-4.43 (m, 2H), 6.73 (bs, 1H), 6.99 (d, 1H), 7.09 (dd, 1H), 7.25-7.20(m, 1H), 7.52 (dd, 1H), 7.74 (d 1H), 7.92 (dd, 1H), 8.22 (s, 1H), 8.42 (d, 1H), 9.02 (bs, 1H) |
| 3-13 |  | 0.33 (AcOEt) | $CDCl_3$: 2.63 (d, 3H), 4.63–4.64 (m, 1H), 7.11(d, 2H), 7.18(dd, 1H), 7.42-7.34(m, 1H), 1.58-7.55(m, 1H), 7.96(d, 1H), 8.07(s, 1H), 8.19-8.10(m, 1H), 8.24(s, 1H), 9.15(s, 1H), 11.6-11.4(m, 1H) |
| 3-14 |  | 0.28 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.63(d, 3H), 3.88(s, 3H), 3.89(s, 3H), 4.47-4.41(m, 1H), 6.60(d, 1H), 6.92(dd, 1H), 7.64(dd, 1H), 7.66-7.61(m, 1H), 7.89(d, 1H), 7.98(dd, 1H), 8.26(s, 1H), 8.43(d, 1H), 8.95(s, 1H) |
| 3-15 |  | 0.30 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.63(d, 3H), 3.66(s, 3H), 3.85(s, 3H), 4.45-4.44(m, 1H), 6.48(dd, 1H), 6.79(d, 1H), 7.64(dd, 1H), 7.97(dd, 2H), 8.26(s, 1H), 8.44(d, 1H), 8.96(s, 1H) |

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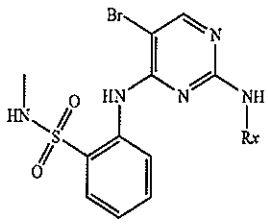
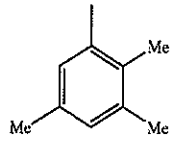
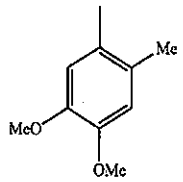
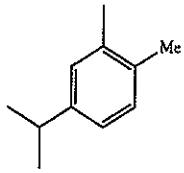
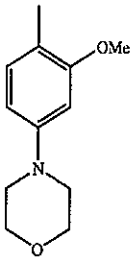
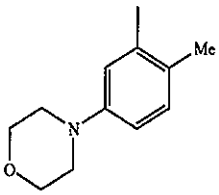
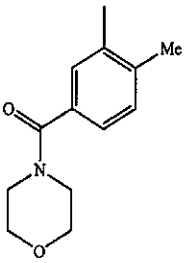


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-16 |  | 0.22 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.17(s, 3H), 2.22(s, 3H), 2.64(s, 3H), 2.63(d, 3H), 4.46-4.44(m, 1H), 6.57(bs, 1H), 7.00(s, 1H), 7.17(dd, 1H), 7.44-7.40(m, 1H), 7.44(s, 1H), 7.93(dd, 1H), 8.19(s, 1H), 8.43(d, 1H), 9.06(s, 1H) |
| 3-17 |  | 0.46 (AcOEt) | $CDCl_3$: 2.22(s, 3H), 2.63(d, 3H), 3.68(s, 3H), 3.89(s, 3H), 4.52-4.47(m, 1H), 6.51(s, 1H), 6.74(s, 1H), 7.12(s, 1H), 7.16-7.12(m, 1H), 7.40(dd, 1H), 7.91(dd, 1H), 8.19(s, 1H), 8.42(d, 1H), 9.12(s, 1H) |
| 3-18 |  | 0.35 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 1.16(d, 6H), 2.25(s, 3H), 2.62(d, 3H), 2.77(t, 1H), 4.49-4.48(m, 1H), 7.00(s, 1H), 7.15(d, 1H), 7.41-7.37(m, 1H), 7.49(d, 2H), 7.54(dd, 1H), 7.92(dd, 1H), 8.21(s, 1H), 8.32(d, 1H), 9.02(s, 1H) |
| 3-19 |  | 0.23 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.63(d, 3H), 3.13-3.10(m, 4H), 3.87(s, 3H), 3.89-3.86(m, 4H), 4.91-4.93(m, 1H), 6.41(dd, 1H), 6.52(d, 1H), 7.24-7.22(m, 1H), 7.32(s, 1H), 7.57(dd, 1H), 7.96(dd, 1H), 8.01(d, 1H), 8.14(s, 1H), 8.44(d, 1H), 8.98(s, 1H) |
| 3-20 |  | 0.36 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.22(s, 3H), 2.64(d, 3H), 3.00-3.2.97(m, 4H), 3.76-3.74(m, 4H), 4.54-4.50(m, 1H), 6.64(d, 1H), 6.66(dd, 1H), 7.11(d, 1H), 7.18(dd, 1H), 7.37(d, 1H), 7.46(dd, 1H), 7.93(dd, 1H), 8.22(s, 1H), 8.42(d, 1H), 9.09(s, 1H) |
| 3-22 |  | 0.27 (AcOEt) | $CDCl_3$: 2.33(s, 3H), 2.65(d, 3H), 3.60-3.45(m, 8H), 4.53-4.49(m, 1H), 6.74(s, 1H), 7.11(d, 1H), 7.22-7.18(m, 1H), 7.58-7.54(m 1H), 7.94(dd, 1H), 8.00(d, 1H), 8.22(s, 1H), 8.37(d, 1H), 9.13(s, 1H) |

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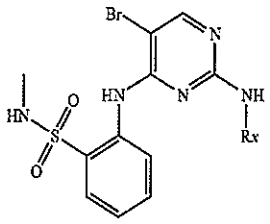
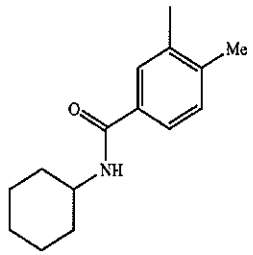
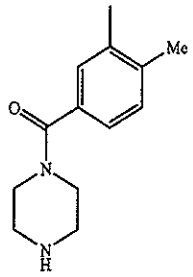
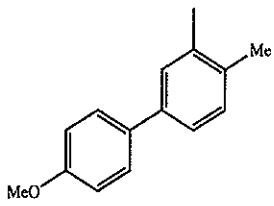
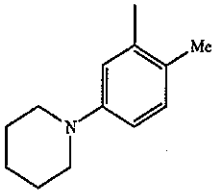
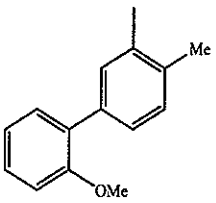


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-23 |  | 0.38 (AcOEt) | $CDCl_3$: 1.24–1.08(m, 2H), 1.46-1.32(m, 2H), 1.76-1.67(m, 2H), 1.98-1.90(m, 2H), 2.33(s, 3H), 2.64(d, 3H), 3.95-3.90(m, 1H), 4.49-4.47(m, 1H), 5.89-5.80(m, 1H), 6.66(s, 1H), 7.15(dd, 1H), 7.48-7.31(m, 2H), 7.91(dd, 1H), 8.12(s, 1H), 8.23(s, 1H), 8.41(d, 1H), 9.18(s, 1H) |
| 3-24 |  | 0.11 (AcOEt) | $CDCl_3$: 2.35(s, 3H), 2.71(s, 3H), 3.07-2.73(m, 2H), 3.86-3.31(m, 6H), 6.85(s, 1H), 7.10(d, 1H), 7.24-7.19(m, 1H), 7.52-7.48(m, 1H), 7.66-7.59(m, 2H), 7.93(d, 1H), 8.06(s, 1H), 8.27-8.21(m, 1H), 8.23(s, 1H), 9.11(s, 1H) |
| 3-25 |  | 0.5 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.52(d, 3H), 2.62(s, 3H), 4.36-4.32(m, 1H), 6.74(s, 1H), 6.87(d, 2H), 7.00-6.91(m, 2H), 7.00-6.97(m, 2H), 7.38(dd, 2H), 7.86(dd, 1H), 7.98(s, 1H), 8.23(s, 1H), 8.28(d, 1H), 9.04(s, 1H) |
| 3-26 |  | 0.45 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 1.62-1.34(m, 6H), 2.13(s, 3H), 2.56(d, 3H), 3.01-2.87(m, 4H), 4.54-4.38(m, 1H), 6.59(s, 1H), 6.69-6.59(m, 1H), 7.02(d, 1H), 7.10-7.07(m, 1H), 7.37(dd, 1H), 7.84(dd, 1H), 8.15(s, 1H), 8.34(d, 1H), 9.01(s, 1H) |
| 3-27 |  | 0.45 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.32(s, 3H), 2.58(d, 3H), 3.75(s, 3H), 4.37-4.44(m, 1H), 6.77-6.73(m, 1H), 6.89-6.82(m 1H), 6.97-6.91(m, 2H), 6.96(d, 1H), 7.20(dd, 1H), 7.25-7.24(m, 1H), 7.33-7.29(m, 1H) |

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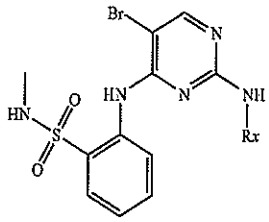
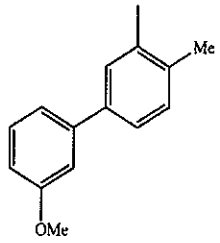
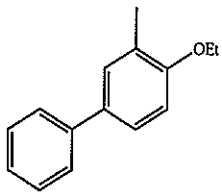
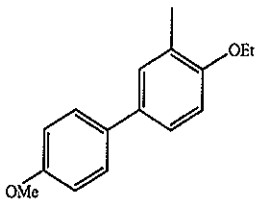
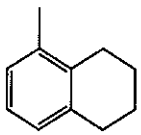
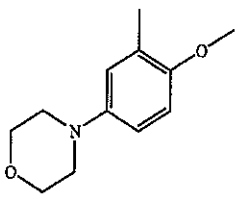
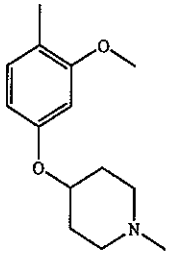



| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-28 |  | 0.35 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.34(s, 3H), 2.64(d, 3H), 3.81(s, 3H), 4.57-4.50(m, 1H), 6.76(bs, 1H), 6.91-6.84(m, 41H), 7.04(d, 1H), 7.83(dd, 1H), 8.06(d, 1H), 8.19(dd, 1H), 8.23(s, 1H), 9.00(s, 1H) |
| 3-29 |  | 0.45 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 1.50(t, 3H), 2.62 (d, 3H), 4.17(dd, 2H), 4.51-4.44(m, 1H), 6.95-6.89(m, 2H), 6.94(d, 1H), 7.16 (dd, 1H), 7.31-7.23(m, 5H), 7.67(s, 1H), 7.11(dd, 1H), 7.23(d, 2H), 7.65(s, 1H), 7.88(dd, 1H), 8.28-8.23(m, 1H), 8.28(s, 1H), 8.43(s, 1H), 8.89(s, 1H) |
| 3-30 |  | 0.45 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 1.49(t, 3H), 2.63(d, 3H), 3.85(s, 3H), 4.16(dd, 2H), 4.55-4.48(m, 1H), 6.81(dd, 1H), 6.95-6.91(m, 3H), 7.11(dd, 1H), 7.23(d, 2H), 7.65(s, 1H), 7.90-7.88(m, 1H), 8.28-8.26(m, 1H), 8.27(s, 1H), 8.39(s, 1H), 8.90(s, 1H) |
| 3-31 |  | 0.29 (n-hexane: AcOEt = 1:1) | $^1$H-NMR: ($CDCl_3$) 1.83-1.72 (4H, m), 2.63 (3H, d), 2.66–2.62(2H, m), 2.80(2H, t), 4.41-4.44(1H, m), 6.64 (1H, br.s), 6.92 (1H, d), 7.09 (1H, dd), 7.18 (1H, dd), 7.45 (1H, dd), 7.59 (1H, dd), 7.92 (1H, d), 8.20 (1H, s), 8.42 (1H, d), 9.08 (1H, br.s). |
| 3-32 |  | 0.3 (n-hexane: AcOEt = 1:1) | DMSO-$d_6$: 2.43(s, 3H), 2.80-2.82(m, 4H), 3.61-3.64 (m, 4H), 3.75(s,3H), 6.62(dd, 1H), 6.93(d, 1H), 7.46(d, 1H), 7.54(dd, 1H), 7.77(dd, 2H), 8.14(bs, 1H), 8.32(s, 1H), 8.38-8.30(m, 1H), 9.14(bs, 1H) |
| 3-33 |  | 0.61 (MeOH: CH2Cl2 = 1:1) | DMSO-$d_6$: 1.59-1.68(m, 2H), 1.88-1.98(m, 2H), 2.13-2.25(m,2H), 2.19(s, 3H), 2.43(s, 3H), 2.60-2.70(m, 2H), 3.75(s, 3H), 4.32-4.40(m, 1H), 6.51 (dd, 1H), 6.64(d, 1H), 7.20(dd, 1H), 7.39(d, 1H), 7.75(dd, 1H), 7.70-7.78(s, 1H), 8.22(s, 1H), 8.26(s, 1H), 8.38-8.41(m, 1H), 9.22(s, 1H) |

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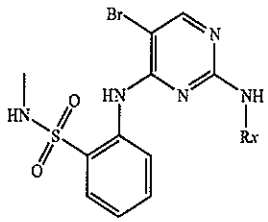
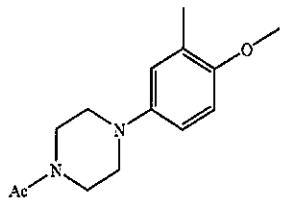
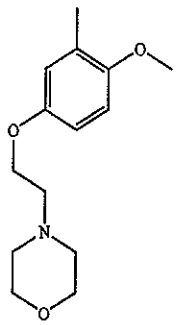
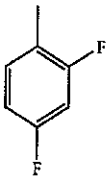
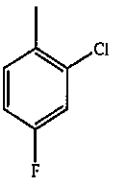
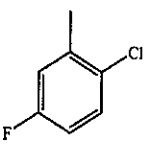


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-34 |  | 0.17 (AcOEt) | $CDCl_3$: 2.11(s, 3H), 2.68(d, 3H), 2.76-2.83(m, 2H), 2.89-2.97(m, 2H), 3.47-3.55(m, 2H), 3.58-3.66(m, 2H), 3.86(s, 3H), 4.70-4.78(m, 1H), 6.53(dd, 1H), 6.81(d, 1H), 7.23(dd, 1H), 7.54-7.62(m, 2H), 7.97(dd, 1H), 8.02-8.03(m, 1H), 8.29(s, 1H), 8.40(d, 1H), 8.99(bs, 1H) |
| 3-35 |  | 0.22 (AcOEt only) | DMSO-$d_6$: 2.40-2.48(m, 7H), 2.63(t, 2H), 3.50-3.58(m, 4H), 3.77(s, 3H), 3.91(t, 2H), 6.60(dd, 1H), 6.93(d, 1H), 7.28(dd, 1H), 7.56(d, 1H), 7.60(dd, 1H), 7.75-7.80(m, 1H), 7.80(dd, 1H), 8.10(s, 1H), 8.35(s, 1H), 8.40(d, 1H), 9.21(s, 1H) |
| 3-36 |  | 0.4 (n-hexane: AcOEt = 1:1) | DMSO-$d_6$: 2.43(s, 3H), 7.03-7.08(m, 1H), 7.21-7.23(m, 1H), 7.25-7.36(m, 1H), 7.47-7.57(m, 2H), 7.74-7.77(m, 2H), 8.28(s, 1H), 8.35(d, 1H), 9.09(s, 1H), 9.24(s, 1H) |
| 3-37 |  | 0.4 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.64(d, 3H), 4.53-4.54(m, 1H), 6.88-6.93(m, 1H), 7.14-7.28(m, 3H), 7.54-7.58(m, 1H), 7.95-7.98(m, 1H), 8.16-8.21(m, 1H), 8.24(s, 1H), 8.33-8.36(m, 1H), 9.05(s, 1H) |
| 3-38 |  | 0.42 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 2.64(d, 3H), 4.46-4.47(m, 1H), 6.63-6.68(m, 1H), 1.30-7.32(m, 2H), 7.55(s, 1H), 7.64-7.68(m, 1H), 7.97-7.99(m, 1H), 8.20-8.39(m, 3H), 9.03(s, 1H) |

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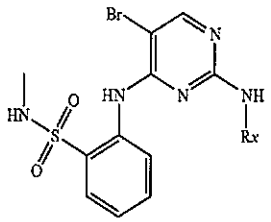
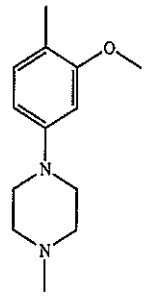
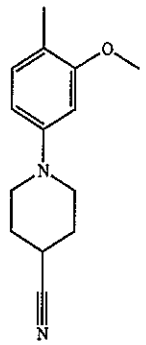
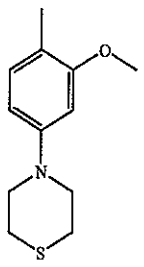
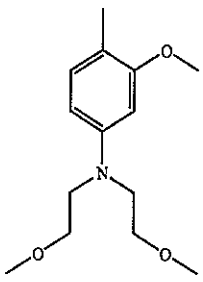


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-39 |  | 562, 564 [M + 1]+ | CDCl3: 2.37(s, 3H), 2.58-2.64(m, 7H), 3.15-3.18(m, 4H), 3.87(s, 3H), 4.60-4.65(m, 1H), 6.43(dd, 1H), G.44-6.54(m, 1H), 7.22(d, 1H), 7.30(s, 1H), 7.57(dd, 1H), 7.94-7.99(m, 2H), 8.18(s, 1H), 8.45(d, 1H), 8.95(s, 1H) |
| 3-40 |  | 572, 574 [M + 1]+ | DMSO-d6: 1.79-1.88(m, 2H), 1.98-2.02(m, 2H), 2.43(s, 3H), 3.02-3.08(m, 3H), 3.28-3.39(m, 2H), 3.76(s, 3H), 6.47(dd, 1H), 6.65(d, 1H), 7.22(dd, 1H), 7.39(d, 1H), 7.45-7.50(m, 1H), 7.74-7.77(m, 2H), 8.18(s, 1H), 8.22(s, 1H), 8.41-8.44(m, 1H), 9.21 (bs, 1H) |
| 3-41 |  | 565, 567 [M + 1]+ | DMSO-d6: 2.44(d, 3H), 2.69-2.71(m, 4H), 3.49-3.52(m, 4H), 3.76(s, 3H), 6.45(dd, 1H), 6.62(d, 1H), 7.23(ddd, 1H), 7.38(d, 1H), 7.46-7.50(m, 1H), 7.72-7.77(m, 2H), 8.19(s, 1H), 8.22(s, 1H), 8.42-8.45(m, 1H), 9.22(s, 1H) |
| 3-42 |  | 595, 597 [M + 1]+ | DMSO-d6: 2.44(s, 3H), 3.31(s, 6H), 3.48-3.53(m, 8H), 3.72(s, 3H), 6.24(dd, 1H), 6.37(d, 1H), 7.18-7.21(m, 2H), 7.40-7.55(m, 1H), 7.72-7.76(m, 2H), 8.17-8.19(m, 2H), 8.40-8.50(m, 1H), 9.23(s, 1H) |

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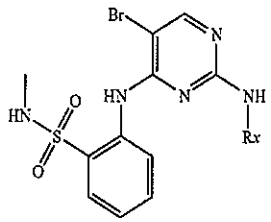
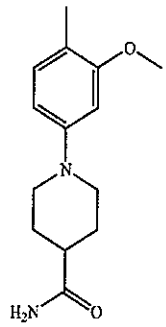
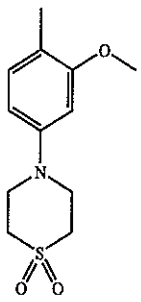
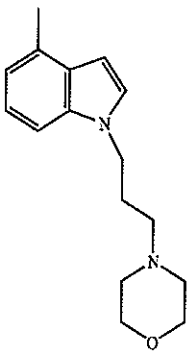


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-43 |  | 590, 592 [M + 1]+ | DMSO-d6: 1.64-1.71(m, 2H), 1.75-1.82(m, 2H), 2.21-2.28(m, 1H), 2.43(d, 3H), 2.62-2.67(m, 2H), 3.68-3.74(m, 2H), 3.76(s, 3H), 6.45(dd, 1H), 6.63(d, 1H), 6.75-6.81(m, 1H), 7.20(ddd, 1H), 7.25-7.30(m, 1H), 7.35(d, 1H), 7.45-7.52Cm, 1H), 7.70-7.77(m, 2H), 8.18(s, 1H), 8.21(s, 1H), 8.40-8.47(m, 1H), 9.22(s, 1H) |
| 3-44 |  | 597, 599 [M + 1]+ | DMSO-d6: 2.44(s, 3H), 3.12-3.17(m, 4H), 3.68-3.85(m, 4H), 3.79(s, 3H), 6.55(dd, 1H), 6.71(d, 1H), 7.19-7.25(m, 1H), 7.43(d, 1H), 7.46-7.53(m, 1H), 7.73-7.78(m, 2H), 8.19-8.22(m, 1H), 8.22(s, 1H), 8.38-8.45(m, 1H), 9.20(bs, 1H) |
| 3-45 |  | 600, 602 [M + 1]+ | DMSO-d6: 1.85-1.95(m, 2H), 2.19(t, 2H), 2.25-2.35(m, 4H), 2.43(s, 3H), 3.52-3.64(m, 4H), 4.19(t, 2H), 6.65(d, 1H), 7.05(dd, 1H), 7.20(d, 1H), 7.23(ddd, 1H), 7.27(d, 1H), 7.40-7.46(m, 1H), 7.42(d, 1H), 7.70-7.75(m, 1H), 7.76(dd, 1H), 8.32(s, 1H), 8.45(d, 1H), 9.22(s, 1H), 9.23(s, 1H) |

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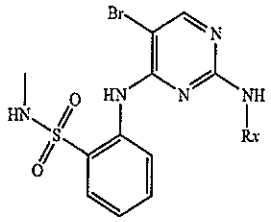
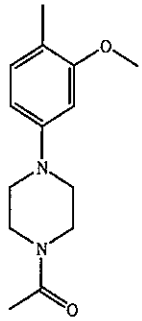
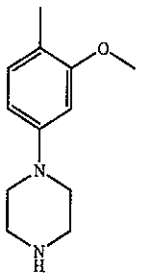
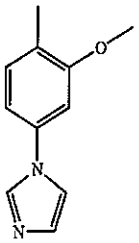
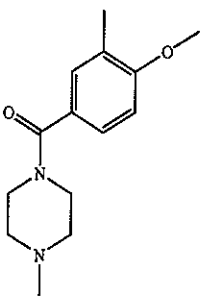


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-46 |  | 590, 592 [M + 1]+ | DMSO-d6: 2.05(s, 3H), 2.44(s, 3H), 3.08-3.17(m, 4H), 3.55-3.63(m, 4H), 3.77(s, 3H), 6.48(dd, 1H), 6.67(d, 1H), 7.23(dd, 1H), 7.41(d, 1H), 7.45-7.52(m, 1H), 7.76(dd, 1H), 7.72-7.78(m, 1H), 8.19(s, 1H), 8.22(s, 1H), 8.40-8.47(m, 1H), 9.22(bs, 1H) |
| 3-47 |  | 548, 550 [M + 1]+ | DMSO-d6: 2.43(s, 3H), 2.82-2.87(m, 4H), 2.99-3.15(m, 4H), 3.76(s, 3H), 6.43(dd, 1H), 6.61(d, 1H), 7.22(dd, 1H), 7.36(d, 1H), 7.43-7.51(m, 1H), 7.75(dd, 1H), 8.17(s, 1H), 8.21(s, 1H), 8.38-8.45(m, 1H), 9.12-9.28(m, 1H) |
| 3-48 |  | MS 530, 532 | CDCl3: 2.65(d, 3H), 3.96(s, 3H), 4.40-4.48(m, 1H), 6.85-6.88(m, 2H), 7.22(d, 1H), 7.25-7.31(m, 1H), 7.56-7.65(m, 3H), 7.79(s, 1H), 8.00(dd, 1H), 8.29(s, 1H), 8.39(dd, 1H), 9.00(s, 1H). |
| 3-49 |  | Rf (AcOEt: MeOH = 9:1) 0.20 | $CDCl_3$: 2.18-2.50(m, 4H), 2.28(s, 3H), 2.65(d, 3H), 3.10-3.75(m, 4H), 3.93(s, 3H), 4.50-4.61(m, 1H), 6.89(d, 1H), 7.06(dd, 1H), 7.59-7.67(m, 2H), 7.93-7.97(m, 1H), 8.26(s, 1H), 8.37-8.43(m, 2H), 9.02(s, 1H). |

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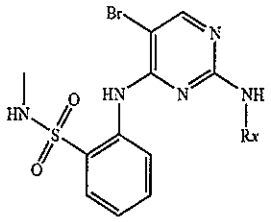
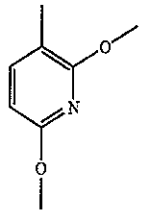
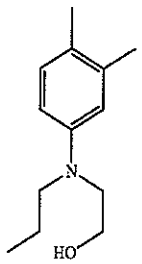
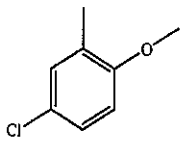
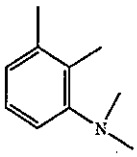
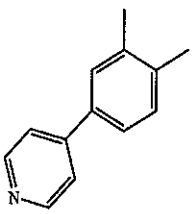
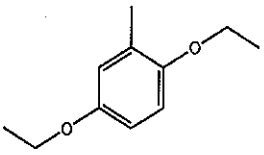


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-50 |  | Rf 0.4 (Hexane/ AcOEt = 1/1) | $CDCl_3$: 2.63(d, 3H), 3.90(s, 3H), 4.00(s, 3H), 4.39-4.47(m, 1H), 6.23(d, 1H), 7.00(s, 1H), 7.22-7.25(m, 1H), 7.57(dd, 1H), 7.96(dd, 1H), 8.22(s, 1H), 8.25 (d, 1H), 8.37(d, 1H), 8.96(s, 1H) |
| 3-51 |  | MS 535, 537 | CDCl3: 1.17(t, 3H), 1.71-1.79(m, 1H), 2.28(s, 3H), 2.62(d, 3H), 3.41(q, 2H), 3.46(t, 2H), 3.79(q, 2H), 4.41-4.48(m, 1H), 6.43(s, 1H), 6.10-6.18(m, 2H), 7.15(dd, 1H), 7.33(d, 1H), 7.35-7.42(m, 1H), 7.90 (dd, 1H), 8.16(s, 1H), 8.45(d, 1H), 9.07(s, 1H). |
| 3-52 |  | Rf | CDCl3: 2.66(d, 3H), 3.91(s, 3H), 4.41-4.47(m, 1H), 6.80(d, 1H), 6.92(dd, 1H), 7.26-7.35(m, 1H), 7.54(s, 1H), 7.76(dd, 1H), 8.00(dd, 1H), 8.27-8.32(m, 2H), 8.38(dd, 1H), 8.97(s, 1H). |
| 3-53 |  | MS 491, 493 | $CDCl_3$: 2.26(s, 3H), 2.62(d, 3H), 2.68(s, 6H), 4.72 (q, 1H), 6.78(s, 1H), 6.89(d, 1H), 7.12(d, 1H), 7.15 (d, 1H), 7.40-7.47(m, 2H), 7.91(dd, 1H), 8.40(s, 1H), 8.41(dd, 1H), 9.11(s, 1H). |
| 3-54 |  | MS 525, 527 | $CDCl_3$: 2.04(s, 3H), 2.65(d, 3H), 4.42-4.48(m, 1H), 6.79(s, 1H), 6.96-7.00(m, 2H), 7.28-7.34(m, 4H), 7.87-7.91(m, 1H), 8.18(s, 1H), 8.23-8.26(m, 2H), 8.53(d, 2H), 9.07(s, 1H). |
| 3-55 |  | Rf (Hexane: AcOEt = 3:1) 0.19 | $CDCl_3$: 1.34(1, 3H), 1.44(t, 3H), 2.63(d, 3H), 3.81(q, 2H), 4.06(q, 2H), 4.46(q, 1H), 6.43(dd, 1H), 6.76(d, 1H), 7.63-7.69(m, 2H), 7.94(d, 1H), 7.98(dd, 1H), 8.42(d, 1H), 8.93(s, 1H). |

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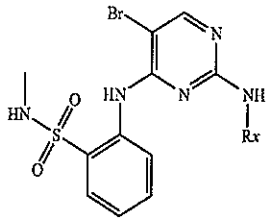
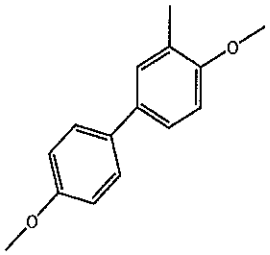
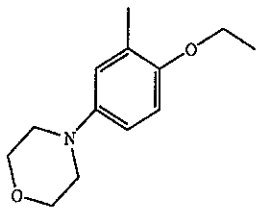
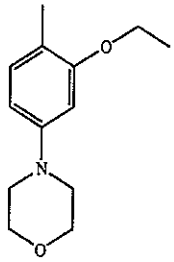
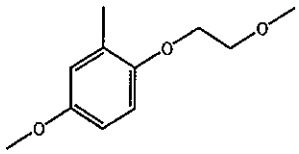
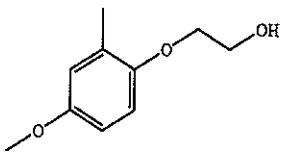
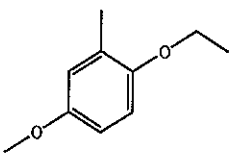


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-56 |  | MS 570, 572 | $CDCl_3$: 2.63(d, 3H), 3.85(s, 3H), 3.93(s, 3H), 4.52 (q, 1H), 6.78-6.83(m, 2H), 6.93(d, 2H), 6390-7.02 (m, 1H), 7.11-7.15(m, 1H), 7.21-7.27(m, 1H), 7.61 (s, 1H), 7.87-7.92(m, 1H), 8.26(s, 1H), 8.20-8.30(m, 1H), 8.38-8.41(m, 1H), 8.92(s, 1H). |
| 3-57 |  | Rf (Hexane: AcOEt = 3:1) 0.16 | $CDCl_3$: 1.44(t, 3H), 2.65(d, 3H), 2.79-2.89(m, 4H), 3.65-3.74(m, 4H), 4.07(q, 2H), 4.52(q, 4H), 6.48 (dd, 1H), 6.80(d, 1H), 7.20-7.25(m, 1H), 7.55-7.67 (m, 2H), 7.92-7.98(m, 2H), 8.29(s, 1H), 8.43(d, 1H), 8.95(s, 1H). |
| 3-58 |  | Rf 0.17 (Hexane/AcOEt = 1/1) | $CDCl_3$: 1.46(t, 3H), 2.63(d, 3H), 3.08-3.13(m, 4H), 3.83-3.90(m, 4H), 4.09(q, 2H), 4.46(q, 1H), 6.39 (dd, 1H), 6.51(d, 1H), 7.21-7.28(m, 1H), 7.37(s, 1H), 7.58(dd, 1H), 7.97(dd, 1H), 8.03(d, 1H), 8.21(s, 1H), 8.46(d, 1H), 8.94(s, 1H). |
| 3-59 |  | MS 538, 540 | $CDCl_3$: 2.63(d, 3H), 3.44(s, 3H), 3.65(s, 3H), 3.69-3.73(m, 2H), 4.10-4.15(m, 2H), 4.40(q, 1H), 6.45 (dd, 1H), 6.85 Cd, 1H), 7.19-7.25(m, 1H), 7.61(dd, 1H), 7.88(s, 1H), 7.93-7.97(m, 2H), 8.27(s, 1H), 8.46(d, 1H), 8.95(s, 1H). |
| 3-60 |  | Rf (AcOEt) 0.54 | $CDCl_3$: 2.63(d, 3H), 3.67(s, 3H), 4.18(t, 2H), 4.38-4.49(m, 3H), 6.46(dd, 1H), 6.81(d, 1H), 7.60-7.69 (m, 2H), 7.92-7.99(m, 2H), 8.27(s, 1H), 8.49(d, 1H), 9.00(s, 1H). |
| 3-61 |  | Rf (Hexane: AcOEt = 2:1) 0.46 | (Hexane: $CDCl_3$: 1.44(t, 3H), 2.63(d, 3H), 3.64(s, 3H), 4.07(q, 2H), 4.47(q, 1H), 6.45(dd, 1H), 6.78(d, 1H), 7.21-7.28(m, 1H), 7.40-7.48(m, 2H), 7.93-7.99(m, 2H), 8.26(s, 1H), 8.44(d, 1H), 8.96(s, 1H). |

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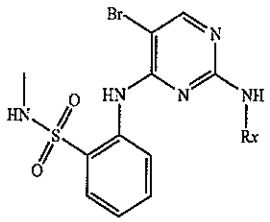
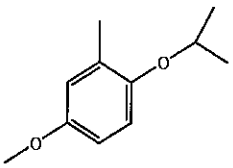
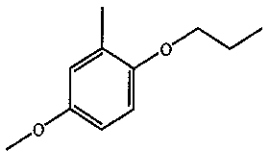
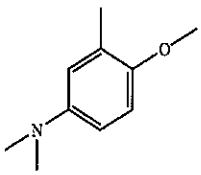
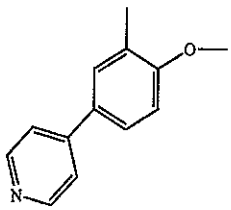
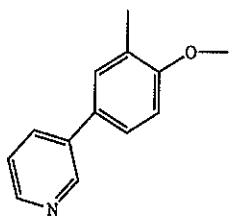
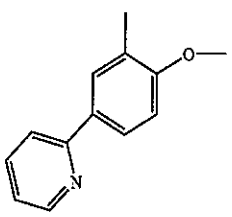


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-62 |  | Rf (Hexane:AcOEt = 3:1) 0.31 | $CDCl_3$: 1.36(d, 6H), 2.63(d, 3H), 3.63(s, 3H), 4.41-4.52(m, 2H), 6.45(dd, 1H), 6.81(d, 1H), 7.21-7.26 (m, 1H), 7.59-7.68(m, 2H), 7.91-7.98(m, 2H), 8.26 (s, 1H), 8.45(d, 1H), 8.96(s, 1H). |
| 3-63 |  | Rf (Hexane: AcOEt = 3:1) 0.40 | $CDCl_3$: 1.07(t, 3H), 1.84(m, 2H), 6.63(d, 3H), 3.64 (s, 3H), 3.96(t, 2H), 4.40-4.49(m, 1H), 6.46(dd, 1H), 6.79(d, 1H), 7.20-7.27(m, 1H), 7.58-7.66(m, 2H), 7.94-7.97(m, 2H), 8.26(s, 1H), 8.45(d. 1H), 8.97(s, 1H). |
| 3-64 |  | Rf (Hexane:AcOEt = 3:1) 0.19 | $CDCl_3$: 2.62(d, 3H), 6.68(s, 6H), 3.84(s, 3H), 4.41-4.48(m, 1H), 6.36(dd, 1H), 6.80(d, 1H), 7.17-7.24 (m, 1H), 7.51-7.62(m, 2H), 7.83(s, 1H), 7.95(dd, 1H), 8.27(s, 1H), 8.3*9-8.45(m, 1H), 8.91(s, 1H). |
| 3-65 |  | Rf (Hexane: AcOEt = 1:1) 0.12 | $CDCl_3$: 2.66(d, 3H), 3.97(s, 3H), 4.47-4.55(m, 1H), 6.96-7.10(m, 3H), 7.21-7.24(m, 1H), 7.66(s, 1H), 7.93(dd, 1H), 8.25(d, 1H), 8.31(s, 1H), 8.47(d, 2H), 8.59(s, 1H), 8.96(s, 1H). |
| 3-66 |  | MS 541, 543 | $CDCl_3$: 2.65(d, 3H), 3.96(s, 3H), 4.61-4.71(m, 1H), 6.89-7.05(m, 3H), 7.16(dd, 1H), 7.15-7.23(m, 1H), 7.60(d, 1H), 7.65(s, 1H), 7.89(d, 1H), 8.21(d, 1H), 8.28(d, 1H), 8.51(br. s, 2H), 8.57(s, 1H), 8.93(s, 1H). |
| 3-67 |  | MS 541, 543 | $CDCl_3$: 2.65(d, 3H), 3.96(s, 3H), 4.51(q, 1H), 6.90-7.06(m, 3H), 7.11-7.16(m, 1H), 7.38(d, 1H), 7.50-7.61(m, 2H), 7.62-7.67(m, 1H), 7.89(dd, 1H), 8.29 (s, 1H), 8.34(d, 1H), 8.53(d, 1 H), 8.79(br.s, 1H), 8.94(s, 1H). |

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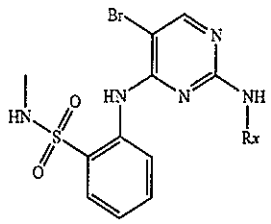
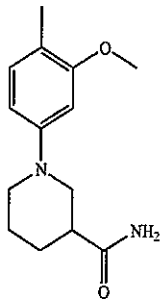
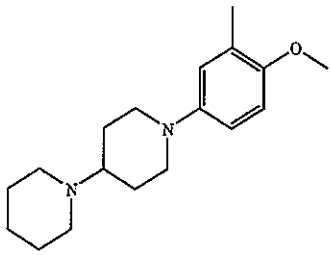
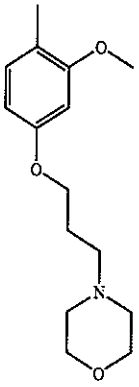


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-68 |  | LC-MS 590 | $CDCl_3$: 1.45-1.59(m, 2H), 1.70-1.78(m, 1H), 1.82-1.90(m, 1H), 2.38-2.50(m, 1H), 2.43(s, 3H), 2.62-2.77(m, 2H), 3.56-3.70(m, 2H), 3.76(s, 3H), 6.46 (dd, 1H), 6.63(d, 1H), 6.82-6.88(br, 1H), 7.22(dd, 1H), 7.31-7.40(m, 2H), 7.43-7.51(m, 1H), 7.50-7.80 (m, 2H), 8.14-8.20 Cbr, 1 H), 8.21(s, 1H), 8.39-8.48 (m, 1H), 9.16-9.26(br, 1) |
| 3-69 |  | 0.34 (CH2Cl2: MeOH = 9:1) | $CDCl_3$: 1.58-1.82(br, 7H), 1.88-2.03(br, 3H), 2.44-2.45(m, 5H), 3.42-3.52(m, 3H), 3.75(s, 3H), 6.66(dd, 1H), 6.92(d, 1H), 7.28(dd, 1H), 7.44(br, 1H), 7.51 (dd, 1H), 7.79-7.81(m, 2H), 8.18(s, 1H), 8.32(s, 1H), 8.35-8.37(m, 1H), 9.17(s, 1H) |
| 3-70 |  | Ms: 607, 609 | DMSO-d6: 1.84-1.92(m, 2H), 2.34-2.41(m, 4H), 2.41-2.45(m, 3H), 2.44(t, 2H), 3.58(t, 4H), 3.75(s, 3H), 4.02(t, 2H), 6.48(dd, 1H), 6.63(d, 1H), 7.21(dd, 1H), 7.41(d, 1H), 7.46(dd, 1H), 7.72-7.78(m, 1H), 7.76(dd, 1H), 8.22(s, 1H), 8.25(s, 1H), 8.40(d, 1H), 9.22(s, 1H) |

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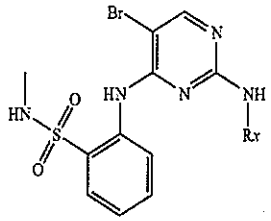
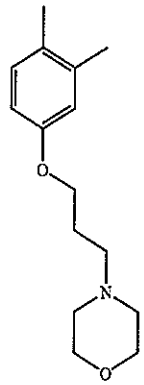
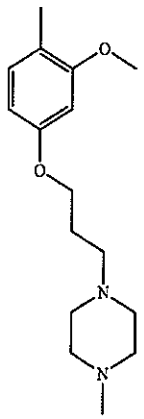
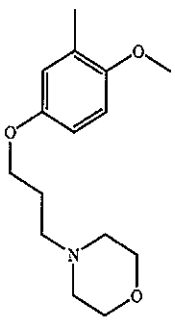


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-71 |  | Ms: 591, 593 | DMSO-d6: 1.84-1.92(m, 2H), 2.14(s, 3H), 2.35-2.4 (m, 4H), 2.43(t, 2H), 2.44(d, 3H), 3.58(t, 4H), 4.01(t, 2H), 6.77(dd, 1H), 6.82(d, 1H), 7.17(dd, 1H), 7.20(d, 1H), 7.3-7.39(m, 1H, 7.71-7.77(m, 2H), 8.2(s, 1H), 8.35-8.44(m, 1H), 8.71(s, 1H), 9.27(s, 1H) |
| 3-72 |  | Ms: 620, 622 | DMSO-d6: 1.82-1.9(m, 2H), 2.13-2.17(m, 3H), 2.25-2.47(m, 13H), 3.75(s, 3H), 4.01(t, 2H), 6.47(dd, 1H), 6.63(d, 1H), 7.19-7.24(m, 1H), 7.41(d, 1H), 7.43-7.5(m, 1H), 7.70-7.79(m, 2H), 8.22(s, 1H), 8.25(brs, 1H), 8.37-8.44(m, 1H), 9.22(s, 1H) |
| 3-73 |  | Ms: 607, 609 | DMSO-d6: 1.78(t, 2H), 2.32-2.36(m, 4H9, 2.35-2.38 (m, 3H), 3.54-3.59(m, 4H), 3.74(t, 3H), 3.78(s, 3H), 6.38-6.42(m, 1H), 6.85(d, 1H), 6.86-6.95(m, 1H), 7.33-7.43(m, 2H), 7.63-7.68(m, 1H), 7.85-8.15(m, 3H), 8.64-8.8(m, 1H). |

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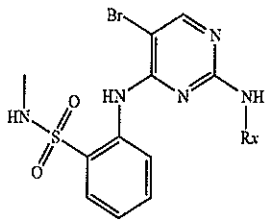
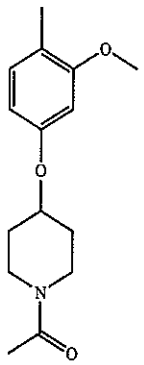
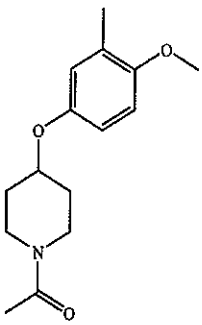
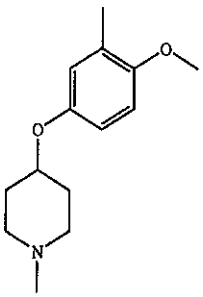
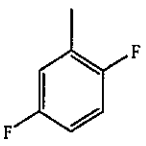


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-74 |  | Ms: 605, 607 | DMSO-d6: 1.47-1.67(m, 2H), 1.84-2.01(m, 2H), 2.03 (s, 3H), 2.41-2.46(m, 3H), 3.23-3.39(m, 2H), 3.65-3.73(m, 1H), 3.81(s, 3H), 3.8-3.88(m, 1H), 4.58-4.65 (m, 1H), 6.55(dd, 1H), 6.68(d, 1H), 7.2-7.26(m, 1H), 7.43(d, 1H), 7.42-7.51(m, 1H), 7.7-7.8(m, 2H), 8.23 (s, 1H), 8.26(brs, 1H), 8.37-8.44(m, 1H), 922(brs, 1H) |
| 3-75 |  | Ms: 605, 607 | DMSO-d6: 1.38-1.6(m, 2H), 1.74-1.9(m, 2H), 2.0(s, 3H), 2.42-2.47(m, 3H), 3.12-3.3(m, 2H), 3.55-3.65 (m, 1H), 3.7-3.8(m, 1H), 3.78(s, 3H), 4.27-4.34(m, 1H), 6.65(dd, 1H), 6.94(d, 1H), 7.24-7.3(m, 1H), 7.53-7.63(m, 2H), 7.74-7.83(m, 2H), 8.09(brs, 1H), 8.35(s, 1H), 8.38(d, 1H), 9.19(brs, 1H) |
| 3-76 |  | Ms: 577, 579 | DMSO-d6: 1.51-1.61(m, 2H), 1.79-1.87(m, 2H), 2.03-2.11(m, 2H), 2.14(s, 3H), 2.42-2.47(m, 3H), 2.52-2.6(m, 2H), 3.77(s, 3H), 4.02-4.09(m, 1H), 6.6 (dd, 1H), 6.92(d, 1H), 7.24-7.3(m, 1H), 7.52-7.6(m, 2H), 7.74-7.82(m, 2H), 8.08(brs, 1H), 8.34(s, 1H), 8.4(d, 1H), 9.2(brs, 1H) |
| 3-77 |  | Rf: 0.4 (n-hexane: AcOEt = 7:3) | DMSO-d6: 2.41-2.45(m, 3H), 6.89-6.96(m, 1H), 6.69(bs, 1H), 7.24-7.33(m, 2H), 7.51-7.57(m, 1H), 7.63-7.7(m, 1H), 7.73-7.78(m, 1H), 7.79(dd, 1H), 8.37(s, 1H), 8.41(d, 1H), 9.21(brs, 1H), 9.24(brs, 1H) |

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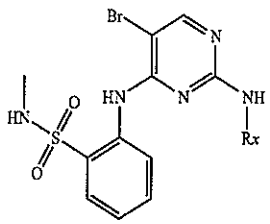
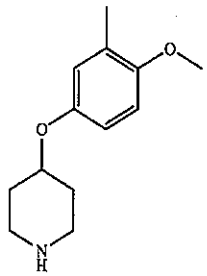
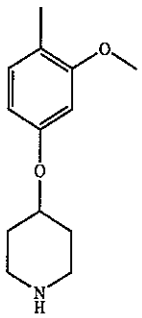
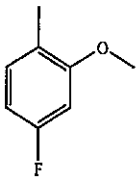
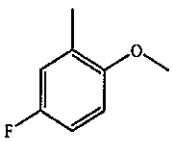
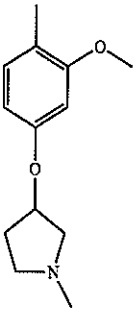


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-78 |  | Ms: 563, 565 | DMSO-d6: 1.33-1.43(m, 2H), 1.79-1.86(m, 2H), 2.43-2.46(m, 3H), 2.46-2.53(m, 2H), 2.87-2.94(m, 2H), 3.77(s, 3H), 4.07-4.14(m, 1H), 6.59(dd, 1H), 6.91(d, 1H), 7.23-7.28(m, 1H), 7.53-7.59(m, 2H), 7.79(dd, 1H), 8.03(brs, 1H), 8.32(s, 1H), 8.38(d, 1H), 8.7-9.5(brs, 1H) |
| 3-79 |  | Ms: 563, 565 | DMSO-d6: 1.41-1.51(m, 2H), 1.88-1.95(m, 2H), 2.41-2.45(m, 3H), 2.54-2.63(m, 2H), 2.92-3.0(m, 2H), 3.75(s, 3H), 4.35-4.43(m, 1H), 6.50(dd, 1H), 6.63(d, 1H), 7.18-7.23(m, 1H), 7.40(d, 1H), 7.42-7.48(m, 1H), 7.75(dd, 1H), 8.21(s, 1H), 8.22-8.25 (m, 1H), 8.37-8.42(m, 1H), 8.9-9.5(brs, 1H) |
| 3-80 |  | Ms: 482, 484 | DMSO-d6: 2.4-2.46(m, 3H), 3.79(s, 3H), 6.72(ddd, 1H), 6.99(dd, 1H), 7.21-7.26(m, 1H), 7.47-7.53(m, 1H), 7.59-7.64(m, 1H), 7.76(dd, 1H), 8.25(s, 1H), 8.29-8.37(m, 2H), 8.8-9.6(m, 1H) |
| 3-81 |  | Ms: 482, 484 | DMSO-d6: 2.41-2.49(m, 3H), 3.82(s, 3H), 6.80(ddd, 1H), 7.01(dd, 1H), 7.3-7.35(m, 1H), 7.56-7.63(m, 1H), 7.7-7.8(m, 1H), 7.82(dd, 1H), 7.85(dd, 1H), 8.16(s, 1H), 8.35(dd, 1H), 9.18(brs, 1H) |
| 3-82 |  | Ms: 563, 565 | DMSO-d6: 1.73-1.82(m, 1H), 2.23-2.34(m, 4H), 2.34-2.42(m, 3H), 2.42-2.46(m, 3H), 2.59(dd, 1H), 2.62-2.68(m, 1H), 2.80(dd, 1H), 3.75(s, 1H), 4.85-4.91(m, 1H), 6.42(dd, 1H), 6.57(d, 1H), 7.19-7.24(m, 1H), 7.41(d, 1H), 7.43-7.51(m, 1H), 7.68-7.79(m, 2H), 8.22(s, 1H), 8.23(s, 1H), 8.37-8.43(m, 1H), 9.21 (brs, 1H). |

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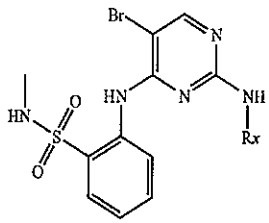
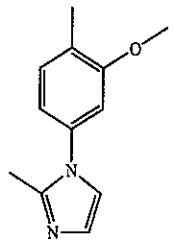
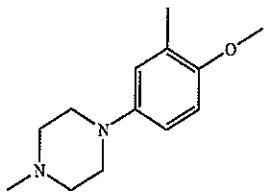


| ExplNo. | Rx | Rf (solvent) or MS | $^1$H-NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 3-83 |  | MS 544, 546 | 2.36(s, 3H), 2.65(d, 3H), 3.93(s, 3H), 4.46-4.51(m, 1H), 6.75-6.80(m, 2H), 6.97-7.04(m, 2h), 7.25-7.30 (m, 1H), 7.56-7.66(m, 2H), 7.98(dd, 1H), 8.29(s, 1H), 8.36-8.44(m, 2H), 9.01(s, 1H). |
| 3-84 |  | MS 562, 564 | CDCl3: 2.32(s, 3H), 2.39-2.47(m, 4H), 2.64(d, 3H), 2.89-2.97(m, 4H), 3.85(s, 3H), 4.54-4.52(m, 1H), 6.52(dd, 1H), 6.79(d, 1H), 7.22(m, 1H), 7.52-7.64 (m, 2H), 7.94-7.99(m, 2H), 8.25(s, 1H), 8.42(d, 1H), 8.93(s, 1H). |

Example 4

2-[5-Bromo-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-propyl-benzenesulfonamides

These compounds are prepared in analogy to Example 2 using 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-propyl-benzenesulfonamide and the corresponding aniline to give compounds No. 4-1 to 4-31 having the substituent Rx as listed under Example 3 for compounds No. 3-1 to 3-31.

Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-propyl-benzenesulfonamide

To a solution of 5-bromo-2,4-dichloropyrimidine (90 μL, 0.70 mmol) and 2-amino-N-propyl-benzenesulfonamide (100 mg, 0.47 mmol), sodium hydride (54.2 mg, 0.56 mmol) in DMSO (1.0 mL) is added and the resulting solution is stirred at 80° C. for 3.0 h. The mixture is poured into water and extracted with ethyl acetate three times. The organic layer is washed with water and then brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane:ethyl acetate=5:1) to afford the title compound as a slightly yellow solid.

$^1$H-NMR (δ, ppm): 0.89 (t, 3H), 1.41 (q, 2H), 3.56 (t, 2H), 4.92 (br.s, 2H), 6.71 (dd, 1H), 6.77 (dd, 1H), 7.33 (dd, 1H), 7.54 (dd, 1H), 8.79 (s, 1H)

Rf (hexane:ethyl acetate=1:1): 0.64.

Example 5

2-[5-Trifluoromethyl-2-(subst. phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamides

These compounds are prepared in analogy to Example 2 using 2-(2-chloro-5-trifluoromethyl-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline to give compounds No. 5-1 to 5-31 having the substituent Rx as listed under Example 3 for compounds No. 3-1 to 3-31.

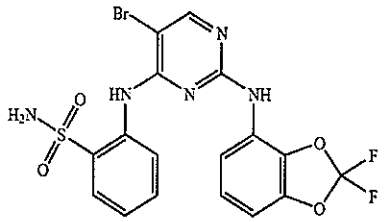
Preparation of 2-(2-chloro-5-trifluoromethyl-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide

To a solution of 2,4-dichloro-5-trifluoromethyl-pyrimidine (386 mg, 1.79 mmol) in acetonitrile (10 mL), 2-amino-N-methyl-benzenesulfonamide (333 mg, 1.79 mmol) and 1,8-diaza[5.4.0]-bicyclo-7-undecene (280 μL, 1.88 mmol) are added successively at ambient temperature. After stirring for 15 h at room temperature, dichloromethane (30 mL) is added to the mixture, and the solution is washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo. The resulting solid is purified by flash chromatography.

$^1$H NMR ($CDCl_3$) δ: 3.73(s, 3H), 6.67-6.69(m, 1H), 6.72-6.73(m, 1H), 7.27-7.31(m, 1H), 7.78 (dd, 1H), 8.60(s, 1H). Rf (hexane:ethyl acetate=1:1): 0.28.

Example 6

2-[5-Bromo-2-(2,3-[difluoromethylenedioxy]phenylamino)-pyrimidin-4-ylamino]-benzenesulonamide



This compound is obtained as a side product formed by N-demethylation on reaction of 2-(5-bromo-2-chloropyrimidin-4-ylamino)-N-methyl-benzenesulfonamide with 2,3-(difluoromethylenedioxy)aniline following the procedure of Example 2. It may also be prepared by reaction of 2-(5-bromo-2-chloropyrimidin-4-ylamino)benzenesulfonamide with 2,3-(difluoromethylenedioxy)aniline.

Rf (n-hexane:ethyl acetate=1:1): 0.46.

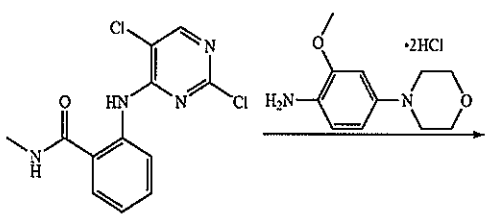
$^1$H-NMR: ($CDCl_3$) 4.83 (bs, 2H), 6.77 (dd, 1H), 6.86 (s, 1H), 6.97 (dd, 1H), 7.31-7.24 (m, 1H), 7.57 (dd, 1H), 7.81 (d, 1H), 8.02 (dd, 1H), 8.28 (d, 1H), 8.29 (s, 1H), 8.88 (s, 1H).

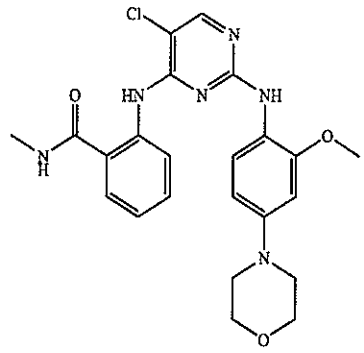
Preparation of 2-(5-bromo-2-chloropyrimidin-4-ylamino) benzenesulfonamide: To a solution of 5-bromo-2,4-dichloropyrimidine (300 mg, 1.32 mmol) and 2-amino-benzenesulfonamide (340 mg, 1.97 mmol) in 2-propanol (3 mL), concentrated hydrochloric acid (0.06 mL) is added and the mixture is stirred at 90° C. for 4.5 hours. The mixture is poured into aqueous sodium hydrogen carbonate and extracted with ethyl acetate three times. The organic layer is washed with water, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by column chromatography (hexane:ethyl acetate=2:1) to afford the title compound.

Rf (hexane:ethyl acetate=1:1): 0.55. $^1$H-NMR (400 MHz, CDCl3) δ: 4.78 (br.s, 2H), 7.22 (dd, 1H), 7.61 (ddd, 1H), 7.95 (dd, 1H), 8.35 (s, 1H), 8.35 (d, 1H), 9.18 (s, 1H).

Example 7A

2-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide

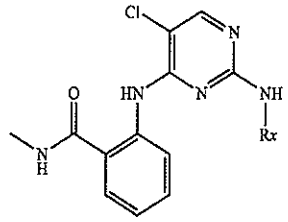


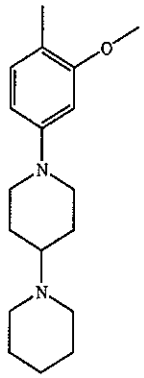
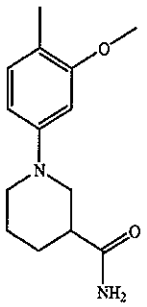
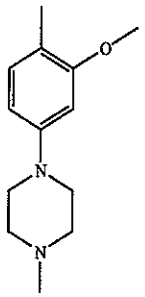


To a suspension of 2-(2,5-dichloro-pyrimidin-4-ylamino)-N-methyl-benzamide (5.05 g, 17.0 mmol) in 90 mL of 2-methoxyethanol are added 2-methoxy-4-morpholinoaniline dihydrochloride (4.56 g, 16.2 mmol) and 17.0 mL of 1N ethanolic solution of hydrogen chloride (17.0 mmol). After the reaction mixture is stirred at 110° C. for 4 hours and cooled to room temperature, the mixture is neutralized with 1N aqueous NaOH solution and extracted with EtOAc (100 mL×3). The organic layer is washed with brine, dried over $Na_2SO_4$ and concentrated under reduced pressure. The resulting black solid is washed with EtOH (90 mL), then purified with silica gel column chromatography ($CH_2Cl_2$ to $CH_2Cl_2$: AcOEt=1:2) to give 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide as a pale yellow solid.

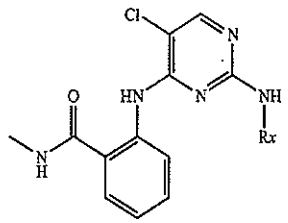
$^1$H-NMR (400 MHz, DMSO-d6,δ): 2.80 (d, 3H, J=4.52 Hz), 3.10-3.20 (m, 4H), 3.78 (s, 3H), 3.70-3.80 (m, 4H), 6.49 (dd, 1H, J=8.56, 2.52 Hz), 6.66 (d, 1H, J=2.52 Hz), 7.08 (dd, 1H, J=8.04, 8.04 Hz), 7.44 (d, 1H, J=8.56 Hz), 7.71 (dd, 1H, J=8.04, 1.48 Hz), 8.10 (s, 1H), 8.13 (s, 1H), 8.59 (d, 1H, J=8.04 Hz) 8.68-8.75 (m, 1H), 11.59 (S, 1H). MS m/z 469, 471 $(M+1)^+$.

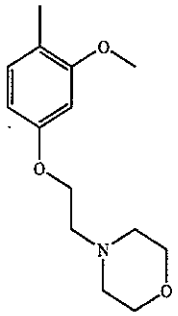
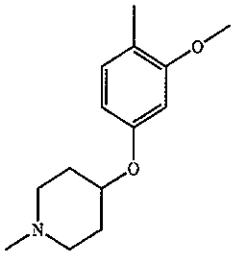
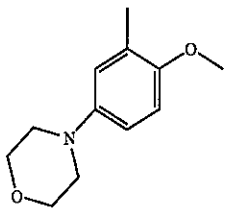
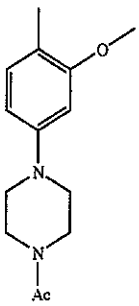
The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-methyl-benzamide and the corresponding aniline following the procedure of Example 7A.



| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 7-1 |  | MS: m/z 550, 552 (M + 1) | DMSO-d6: 1.44-1.33(m, 2H), 1.64-1.45(m, 6H), 1.73-1.89(m, 2H), 2.34-2.44(m, 1H), 2.43-2.55(m, 4H), 2.55(t, 2H), 2.80(d, 3H), 3.75(s, 3H), 3.72-3.75 (m, 2H), 6.48(dd, 1H), 6.62(d, 1Hl), 7.06(dd, 1H), 7.32(dd, 1H), 7.39(d, 1H), 7.71(dd, 1H), 8.09(s, 1H), 8.60(d, 1H), 8.70(d, 1H), 11.58(s, 1H) |
| 7-2 |  | 0.3 (MeOH: AcOEt = 5:95) | $CDCl_3$: 1.70-1.97(m, 4H), 2.62-2.79(m, 1H), 3.04(d, 3H), 3.02-3.18(m, 2H), 3.23-3.33(m, 2H), 3.88(s, 3H), 5.39-5.47(m, 1H), 6.15-6.24(m, 1H), 6.55-6.62(m, 2H), 6.74-6.82(m 1H), 7.09(dd, 1H), 7.23-7.32(m, 1H), 7.46-7.52(m, 2H), 8.09(s, 1H), 8.15(d, 1H), 8.68(d, 1H) 11.0(bs, 1 |
| 7-3 |  | MS (ESI) m/z 482, 484 $(M + 1)^+$ | DMSO-d6: 2.24(s, 3H), 2.45-2.55(m, 4H), 2.80(d, 3H, J=4.52 Hz), 3.12-3.17(m, 4H), 3.76(s, 3H), 6.48 (dd, 1H, J=8.56, 2.52 Hz), 6.63(d, 1H, J=2.52 Hz), 7.05-7.10(m, 1H), 7.27-7.35(m, 1H), 7.40(d, 1H, J= 8.56 Hz), 7.69-7.72(m, 1H), 8.09(S, 1H), 8.12(s, 1H), 8.55-8.65(m, 1H), 8.67-8.75(m, 1H), 11.59(s, 1H) |

-continued



| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 7-4 |  | 0.46 (MeOH: $CH_2Cl_2$ = 1:4) | DMSO-d6: 2.48-2.55(m, 4H), 2.71(t, 2H), 2.80(d, 3H), 3.58-3.61(m, 4H), 3.76(s, 3H), 4.11(t, 2H), 6.52(dd, 1H), 6.66(d, 1H), 7.06(dd, 1H), 7.32(dd, 1H), 7.46(d, 1H), 7.71(dd, 1H), 8.11(s, 1H), 8.19(s, 1H), 8.54-8.60(m, 1H), 8.60-8.75(m, 1H), 11.6(s, 1H) |
| 7-5 |  | m/z 497, 499 $(M + 1)^+$ | DMSO-d6: 1.60-1.70(m, 2H), 1.90-1.98(m, 2H), 2.13-2.25(m, 2H), 2.19(s, 3H), 2.60-2.67(m, 2H), 2.80(d, 3H, J=4.52 Hz), 3.75(s, 3H), 4.30-4.40(m, 1H), 6.54(dd, 1H, J=8.56, 2.0 Hz), 6.65(d, 1H, J= 2.0 Hz), 7.04-7.09(m, 1H), 7.25-7.35(m, 1H), 7.43(d, 1H, J=8.56 Hz), 7.68-7.73(m, 1H), 8.10(s, 1H), 8.18 (s, 1H) 8.52-8.59(m, 1H), 8.68-8.75(m, 1H), 11.57(s, 1H) |
| 7-6 |  | 0.25 (n-hexane: AcOEt = 1:2) | $CDCl_3$: 2.95(m, 4H), 3.03(d, 3H), 3.75(m, 4H), 3.86 (s, 3H), 6.21-6.19(br, 1H), 6.49(dd, 1H), 6.50(d, 1H), 7.09-7.05(m, 1H), 7.50(dd, 1H), 8.08(d, 1H), 8.13 (s, 1H), 8.68(d, 1H), 11.07(s, 1H) |
| 7-7 |  | MS m/z 510, 512 (M + 1) | DMSO-d6: 2.06(s, 3H), 2.80(d, 3H), 3.11(t, 2H), 3.16(t, 2H), 3.60(dd, 4H), 3.77(s, 3H), 6.51(dd, 1H), 6.68(d, 1H), 7.08(dd, 1H), 7.33(dd, 1H), 7.46(d, 1H), 7.71(d, 1H), 8.10(s, 1H), 8.12(s, 1H), 8.59-8.61 (m, 1H), 8.70-8.71(m, 1H), 11.59(s, 1H) |

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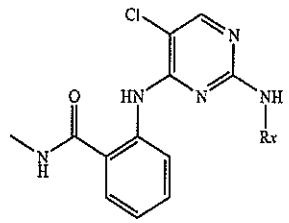
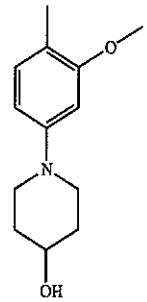
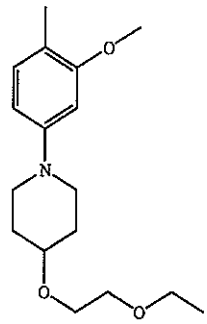
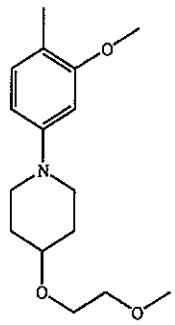
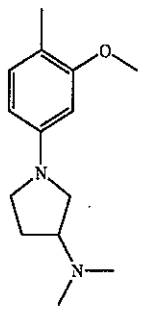
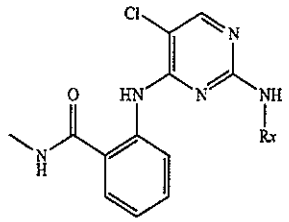
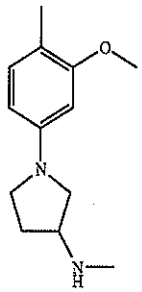
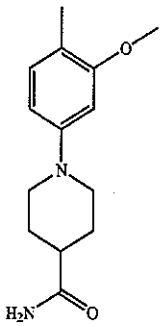
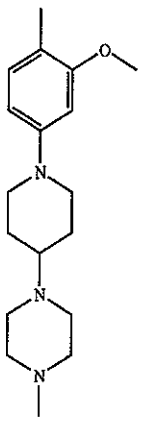


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 7-8 |  | 0.48 (MeOH: AcOEt = 5:95) | $CDCl_3$: 1.46(d, 1H), 1.68-1.82(m, 2H), 2.02-2.09(m, 2H), 2.83-2.96(m, 2H), 3.03(d, 3H), 3.44-3.53(m, 2H), 3.82-3.92(m, 1H), 3.87(s, 3H), 6.15-6.23(m, 1H), 6.51 (d, 1H), 6.56(bs, 1H), 7.07(dd, 1H), 7.48(d, 2H), 8.08(s, 1H), 8.08-8.10(m, 1H), 8.69(d, 1H), 11.0(bs, 1H) |
| 7-9 |  | 0.4 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 1.22(t, 3H), 1.73-1.85(m, 2H), 2.00-2.09(m, 2H), 2.81-2.90(m, 2H), 3.03(d, 3H), 3.41-3.56(m, 3H), 3.56(dd, 2H), 3.58-3.62(m, 2H), 3.64-3.68(m, 2H), 3.86(s, 3H), 6.15-6.24(m, 1H), 6.50(dd, 1H), 6.56(d, 1H), 7.07(dd, 1H), 7.24-7.30(m, 1H), 7.45-7.52(m, 2H), 8.08(s, 1H), 8.06-8.08(m, 1H), 8.69(d, 1H), 11.0(bs, 1H) |
| 7-10 |  | 0.4 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 1.73-1.85(m, 2H), 2.01-2.10(m, 2H), 2.82-2.90(m, 2H), 3.03(d, 3H), 3.41(s, 3H), 3.45-3.51(m, 2H), 3.56-3.58(m, 2H), 3.65-3.68(m, 2H), 3.86(s, 3H), 6.14-6.22(m, 1H), 6.50(dd, 1H), 6.56(d, 1H), 7.07(dd, 1H), 7.23-7.30(m, 1H), 7.44-7.52(m, 2H), 8.08(s, 1H), 8.06-8.08(m, 1H), 8.69(d, 1H), 11.0(bs, 1H) |
| 7-11 |  | 0.54 (MeOH: $CH_2Cl_2$ = 1:4) | DMSO-d6: 1.78-1.89(m, 1H), 2.13-2.22(m, 1H), 2.22(s, 6H), 2.77-2.87(m, 1H), 2.79(d, 3H), 3.04-3.10(m, 1H), 3.23-3.50(m, 3H), 3.75(s, 3H), 6.11(dd, 1H), 6.22(d, 1H), 7.05(dd1H), 7.21-7.32(m, 1H), 7.26(d, 1H), 7.70(d, 1H), 8.06(s, 1H), 8.08(s, 1H), 8.57-8.66(m, 1H), 8.66-8.73(m, 1H), 11.6(s, 1H) |

-continued



| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 7-12 |  | 0.27 (MeOH: $CH_2Cl_2$ = 1:1) | DMSO-d6: 1.77-1.87(m, 1H), 2.09-2.18(m, 1H), 2.35(s, 3H), 2.79(d, 1H), 3.02-3.07(m, 1H), 3.23-3.50(m, 4H), 3.74(s, 3H), 6.09(dd, 1H), 6.20(d, 1H), 7.04(dd, H), 7.22-7.32(m, 1H), 7.26(d, 1H), 7.70(d, 1H), 8.05(s, 1H), 8.08(s, 1H), 8.57-8.67(m, 1H), 8.67-8.73(m, 1H), 11.6(s, 1H) |
| 7-13 |  | 0.23 (MeOH: AcOEt = 5:95) | $CDCl_3$: 1.62-1.74(m, 3H), 1.76-1.85(m, 2H), 2.00-2.09(m, 2H), 2.20-2.31(m, 1H), 2.64-2.69(m, 2H), 2.79(d, 3H), 3.56-4.04(m, 2H), 4.04(s, 3H), 6.49(dd, 1H), 6.63(d, 1H), 6.78(bs, 1H), 7.07(dd, 1H), 7.28-7.38(m, 1H), 7.39(d, 1H), 7.71(d, 1H), 8.09-8.11(m, 2H), 8.09(s, 1H), 8.60(d, 1H), 8.71(d, 1H), 11.6(bs, 1H) |
| 7-14 |  | 0.30 (MeOH: $CH_2Cl_2$ = 4:1) | DMSO-d6: 1.61-1.46(m, 2H), 1.92-1.82(m, 2H), 2.14(s, 3H), 2.41-2.23(m, 5H, 2.60-2.45(m, 4H), 2.67(t, 2H), 2.79(d, 3H), 3.75(s, 3H), 3.71-3.75(m, 2H), 6.48(dd, 1H), 6.63(d, 1H), 7.10-7.03(m, 1H), 7.34-7.27(m, 1H), 7.43-7.35(m, 1H), 7.71(dd, 1H), 8.09(s, 1H), 8.11(bs, 1H), 8.65-8.56(m, 1H), 8.75-8.67(m, 1H), 11.6(s, 1H) |

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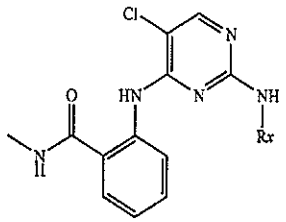
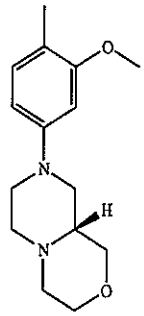
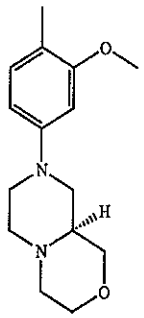
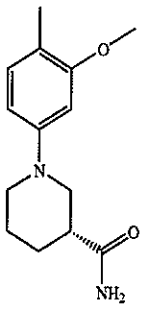
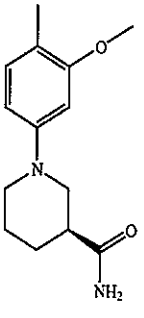


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 7-15 |  | MS (ESI) m/z 524, 526 (M + 1)+ | DMSO-d6: 2.19-2.37(m, 4H), 2.65-2.85(m, 3H), 2.80(d, 3H, J=4.5 Hz), 3.15-3.21(m, 1H), 3.48-3.59 m, 2H), 3.61-3.67(m, 1H), 3.72-3.81(m, 1H), 3.76 (s, 3H), 6.47(dd, 1H, J=8.6, 2.5 Hz), 6.65(d, 1H, J= 2.5 Hz), 7.04-7.10(m, 1H), 7.28-7.35(m, 1H), 7.42(d, 1H, J=8.6 Hz), 7.69-7.74(m, 1H), 8.09(s, 1H), 8.12 (s, 1H), 8.55-8.63(m, 1H), 8.68-8.73(m, 1H), 11.60 (s, 1H) |
| 7-16 |  | MS (ESI) m/z 524, 526 (M + 1)+ | DMSO-d6: 2.19-2.37(m, 4H), 2.65-2.85(m, 3H), 2.80 (d, 3H, J=4.5 Hz), 3.15-3.21(m, 1H), 3.48-3.59(m, 2H), 3.61-3.67(m, 1H), 3.72-3.81(m, 1H), 3.76(s, 3H), 6.47(dd, 1H, J=8.6, 2.5 Hz), 6.65(d, 1H, J= 2.5 Hz), 7.04-7.10(m, 1H), 7.28-7.35(m, 1H), 7.42(d, 1H, J=8.6 Hz), 7.69-7.74(m, 1H), 8.09(s, 1H), 8.12 (s, 1H), 8.55-8.63(m, 1H), 8.68-8.73(m, 1H), 11.60 (s, 1H) |
| 7-17 |  | MS 510 | DMSO-d6: 0.98(t, 3H), 1.81-1.71(m, 3H), 1.95-1.84 (m, 3H), 2.68-2.63(m, 1H), 2.80(d, 3H), 3.12-3.08(m, 4H), 3.28(d, 2H), 3.76(s,3H), 6.50(dd, 1H), 6.64(d, 1H), 6.86(bs, 1H), 7.07(dd, 1H), 7.46-7.19(m, 3H), 7.71(d, 1H), 8.09(s, 1H), 8.15-8.10(m, 1H), 8.66-8.58(m, 1H), 8.77-8.70(m, 1H), 11.6(s, 1H) |
| 7-18 |  | MS 510 | DMSO-d6: 0.98(t, 3H), 1.81-1.71(m, 3H), 1.95-1.84 (m, 3H), 2.68-2.63(m, 1H), 2.80(d, 3H), 3.12-3.08(m, 4H), 3.28(d, 2H), 3.76(s,3H), 6.50(dd, 1H), 6.64(d, 1H), 6.86(bs, 1H), 7.07(dd, 1H), 7.46-7.19(m, 3H), 7.71(d, 1H), 8.09(s, 1H), 8.15-8.10(m, 1H), 8.66-8.58(m, 1H), 8.77-8.70(m, 1H), 11.6(s, 1H) |

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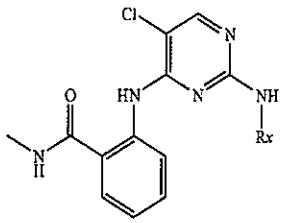
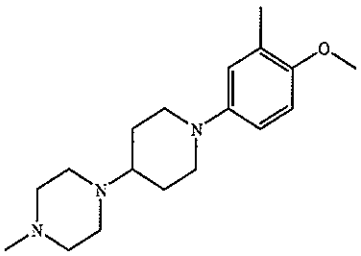
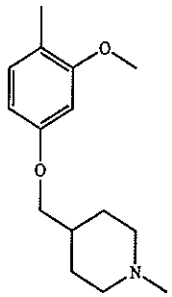
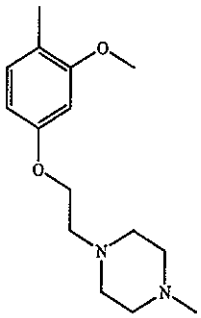
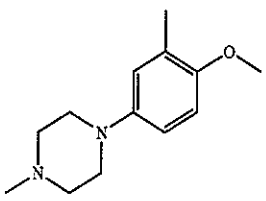


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 7-19 |  | 0.16 (CH2Cl2:MeOH = 9:1) | 1.40-1.53(m, 2H), 1.72-1.80(m, 2H), 2.18(s, 3H), 2.19-2.44(m, 5H), 2.80(d, 3H), 3.46(m, 2H), 3.74(s, 3H), 6.65(dd, 1H), 6.91(d, 1H), 7.07-7.10(m, 1H), 7.36-7.40(m, 1H), 7.45-7.49(m, 1H), 7.73(dd, 1H), 8.12(s, 1H), 8.18(S, 1H), 8.61(d, 1H), 8.72-8.77(m, 1H), 11.68(s, 1H) |
| 7-20 |  | Ms: 511 | 1.25-1.37(m, 2H), 1.62-1.79(m, 3H), 1.81-1.9(m, 2H), 2.16(s, 3H), 2.75-2.85(m, 5H), 3.76(s, 3H), 3.8-3.88(m, 2H), 6.45-6.55(m, 1H), 6.6-6.67(m, 1H), 7.02-7.12(m, 1H), 7.25-7.35(m, 1H), 7.4-7.5(m, 1H), 7.67-7.78(m, 1H), 8.1(s, 1H), 8.19(brs, 1H) 8.5-8.62 (m, 1H), 8.66-8.8(m, 1H), 11.6(s, 1H) |
| 7-21 |  | Ms: 526 | 2.17(s, 3H), 2.29-2.39(m, 3H), 2.45-2.56(m, 4H), 2.7 (t, 2H), 3.76(s, 3H), 4.09(t, 2H), 6.52(dd, 1H), 6.66 (d, 1H), 7.06(dd, 1H), 7.31(dd, 1H), 7.45(d, 1H), 7.71(dd, 1H), 8.1(S, 1H), 8.19(s, 1H), 8.5-8.6(m, 1H), 8.67-8.75(m, 1H), 11.6(s, 1H) |
| 7-22 |  | Ms: 482 | 2.24(s, 3H), 2.42-2.5(m, 4H), 2.8(d, 3H), 2.94-3.0 (m, 4H), 3.74(S, 3H), 6.65(dd, 1H), 6.93(d, 1H), 7.07-7.14(m, 1H), 7.34-7.4(m, 1H), 7.45(d, 1H), 7.73(dd, 1H), 8.14(s, 1H), 8.18(s, 1H), 8.61(dd, 1H), 8.7-8.77(m, 1H), 11.7(s, 1H) |

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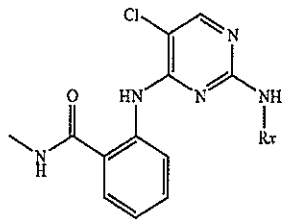
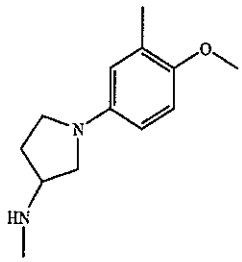
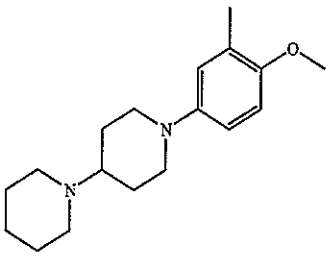
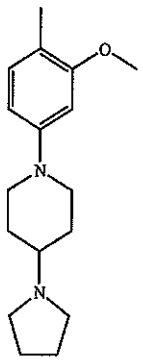
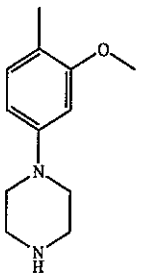


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 7-23 |  | Ms: 482 | 1.67-1.76(m, 1H), 2.0-2.1(m, 1H), 2.25-2.31(m, 3H), 2.8(d, 3H), 2.85-2.91(m, 1H), 3.04-3.12(m, 1H), 3.14-3.3(m, 3H), 3.7(s, 3H), 6.26(dd, 1H), 6.91(d, 1H), 7.01-7.04(m, 1H), 7.07(dd, 1H), 7.32(dd, 1H), 7.72(d, 1H), 8.14(s, 1H), 8.17(s, 1H), 8.63(d, 1H), 8.7-8.78(m, 1H), 11.6(s, 1H) |
| 7-24 |  | Ms: 550 | 1.35-1.57(m, 8H), 1.7-1.78(m, 2H), 2.81(d, 3H), 3.46-3.52(m, 2H), 3.74(s, 3H), 6.65(dd, 1H), 6.91(d, 1H), 7.05-7.12(m, 1H), 7.34-7.42(m, 1H), 7.46(d, 1H), 7.73(dd, 1H), 8.11(s, 1H), 8.18(s,1H), 8.62 (dd, 1H), 8.71-8.78(m, 1H), 11.7(s, 1H) |
| 7-25 |  | 536 [M + 1]+ | DMSO-d6: 1.48-1.58(m, 2H), 1.65-1.72(m, 4H), 1.90-1.97(m, 2H), 2.07-2.14(m, 1H), 2.49-2.55(m, 4H), 2.70-2.77(m, 2H), 2.79(d, 3H), 3.60-3.65(m, 2H), 3.75(s, 3H), 6.48(dd, 1H), 6.63(d, 1H), 7.03-7.09(m, 1H), 7.28-7.34(m, 1H), 7.39(d, 1H), 7.71(dd, 1H), 8.09(s, 1H), 8.11(s, 1H), 8.55-8.65(m, 1H), 8.69-8.73(m, 1H), 11.59(s, 1H) |
| 7-26 |  | 468 [M + 1]+ | DMSO-d6: 2.80(d, 3H), 2.84-2.89(m, 4H), 3.04-3.08(m, 4H), 3.76(s, 3H), 6.47(dd, 1H), 6.62(dd, 1H), 7.04-7.10(m, 1H), 7.28-7.35(m, 1H), 7.40(d, 1H), 7.69-7.73(m, 1H), 8.09(s, 1H), 8.12(s, 1H), 8.55-8.63(m, 1H), 8.68-8.73(m, 1H), 11.59(s, 1H) (an aliphatic NH is hidden) |

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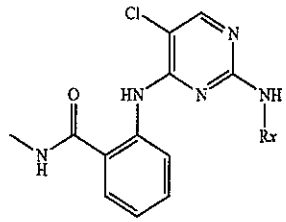
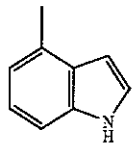
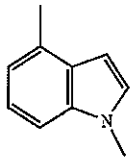
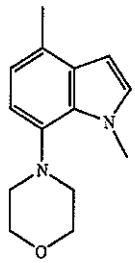
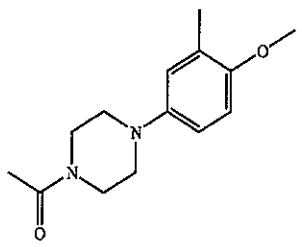
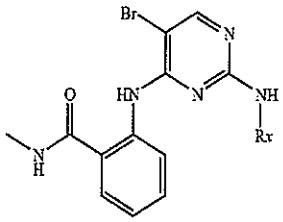
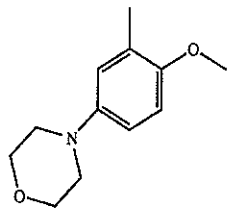
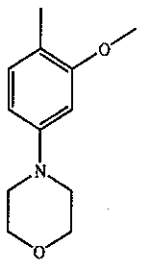
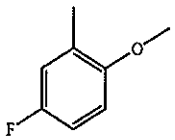
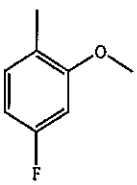


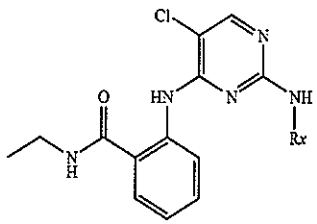
| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 7-27 |  | 393 [M + 1]+ | DMSO-d6: 2.80(d, 3H), 6.64-6.67(m, 1H), 7.01-7.08(m, 2H), 7.15(d, 1H), 7.24-7.29(m, 2H), 7.44(d, 1H), 7.69-7.73(m, 1H), 8.20(s, 1H), 8.65-8.73(m, 2H), 9.15(s, 1H), 11.06(s, 1H), 11.63(s, 1H) |
| 7-28 |  | 407 [M + 1]+ | DMSO-d6: 2.81(d, 3H), 3.79(s, 3H), 6.67(d, 1H), 7.05-7.10(m, 1H), 7.12(d, 1H), 7.17(d, 1H), 7.23(d, 1H), 7.25-7.30(m, 1H), 7.50(d, 1H), 7.70-7.73(m, 1H), 8.20(s, 1H), 8.67(d, 1H), 8.70–8.75(m, 1H), 9.17(s, 1H), 11.64(s, 1H) |
| 7-29 |  | 492 [M + 1]+ | DMSO-d6: 2.80(d, 3H), 2.91-2.99(m, 4H), 3.65-3.81(m, 2H), 3.82-3.95(m, 2H), 4.12(s, 3H), 6.58(d, 1H), 6.90(d, 1H), 7.05-7.09(m, 1H), 7.14(d, 1H), 7.22-7.28(m, 1H), 7.30(d, 1H), 7.70(dd, 1H), 8.16(s, 1H), 8.63-8.67(m, 1H), 8.68-8.72(m, 1H), 9.06(s, 1H), 11.64(s, 1) |
| 7-30 |  | MS m/z 510 | DMSO-$d_6$: 2.02(s, 3H), 2.80(d, 3H), 2.82-2.92(m, 2H), 2.92-3.01(m, 2H), 3.44-3.53(m, 4H), 3.76(s, 3H), 6.68(dd, 1H), 6.95(d, 1H), 7.09(dd, 1H), 7.35-7.40(m, 1H), 7.50(brs, 1H), 7.73(d, 1H), 8.15(s, 1H), 8.19(s, 1H), 8.59(d, 1H), 8.69-8.76(m, 1H), 11.66(s, 1H). |

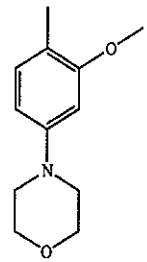
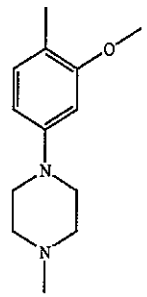
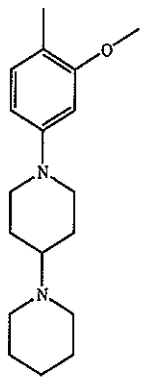
The following 2-[5-Bromo-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-ethyl-benzamide are prepared from 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-ethyl-benzamide and the corresponding aniline following the procedure of Example 7A



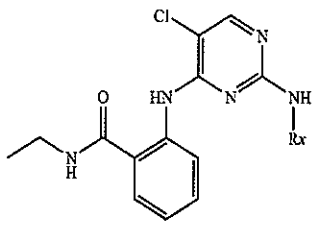

| Expl No. | Rx | Rf (solvent) or MS | NMR |
|---|---|---|---|
| 8-1 |  | 0.27 (n-hexane: AcOEt = 1:2) | DMSO-d6: 2.80(d, 3H), 2.88(t, 4H), 3.65(m, 4H), 3.75 (s, 3H), 6.64(dd, 1H), 6.94(d, 1H), 7.11-7.08(m, 1H), 7.38-7.34(m, 1H), 7.47-7.46(m, 1H), 7.70(dd, 1H), 8.11(s, 1H), 8.26(s, 1H), 8.51-8.49(m, 1H). 8.72–8.71(m, 1H), 11.41(s, 1H) |
| 8-2 |  | m/z 513, 515 (M + 1) | DMSO-d6: 2.79(d, 3H, J=4.04 Hz), 3.10-3.20(m, 4H), 3.77(s, 3H), 3.70-3.80(m, 4H), 6.45-6.55(m, 1H), 6.63-6.69(m, 1H), 7.05-7.10(m, 1H), 7.28-7.34 (m, 1H), 7.40-7.45(m, 1H), 7.65–7.70(m, 1H), 8.13 (s, 1H), 8.16(s, 1H), 8.50-8.56(m, 1H) 8.65-8.72(m, 1H), 11.40(s, 1H) |
| 8-3 |  | 0.48 (n-Hexane: AcOEt = 4:1) | DMSO-d6: 2.80(d, 3H), 3.83(s, 3H), 4.11(t, 2H), 6.82(ddd, 1H), 7.03(dd, 1H), 7.15(dd, 1H), 7.44(dd, 1H), 7.73(d, 1H), 7.93(dd, 1H), 8.13(s, 1H), 8.33(s, 1H), 8.50(d, 1H), 8.70–8.77(m, 1H), 11.3(s, 1). |
| 8-4 |  | MS 446, 448 | 2.79(d, 3H), 3.79(s, 3H), 6.75(ddd, 1H), 7.0(dd, 1H), 7.05-7.12(m, 1H), 7.3-7.36(m, 1H), 7.62(dd, 1H), 7.69(dd, 1H), 8.2(s, 1H), 8.29(s, 1H), 8.45(d, 1H), 8.66-8.73(m, 1H), 11.4(brs, 1H). |

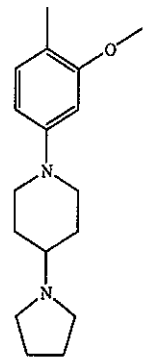
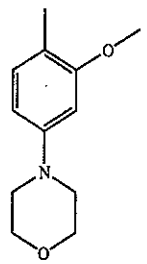
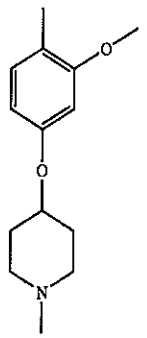
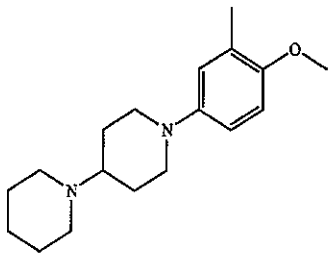
The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-N-ethyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-ethyl-benzamide and the corresponding aniline following the procedure of Example 7A



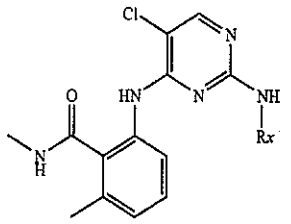
| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 9-1 |  | 0.35 (n-hexane: AcOEt = 1:2) | $CDCl_3$: 1.27(t, 3H), 3.10-3.15(m, 4H), 3.47-3.58(m, 2H), 3.85-3.93(m, 4H), 3.89(s, 3H), 6.08-6.17(m, 1H), 6.48(dd, 1H), 6.53(d, 1H), 7.05-7.11(m, 1H), 7.42-7.53(m, 2H), 8.08(s, 1H), 8.12(d, 1H), 8.67(d, 1H), 10.94(brs, 1H). |
| 9-2 |  | MS (ESI) m/z 497, 499 (M + 1)$^+$ | $CDCl_3$: 1.26(t, 3H, J=7.56 Hz), 2.37(s, 3H), 2.57-2.62(m, 4H), 3.15-3.20(m, 4H), 3.49(dq, 2H, J=7.56, 1.52 Hz), 3.87(s, 3H), 6.11-6.16(m, 1H), 6.49 (dd, 1H, J=8.56, 2.52 Hz), 6.55(d, 1H, J=2.52 Hz), 7.05-7.10(m, 1H), 7.23(s, 1H), 7.41-7.50(m, 2H), 8.07(s, 1H), 8.08 (d, 1H, J=8.56 Hz), 8.65-8.69(m, 1H), 10.93(s, 1H) |
| 9-3 |  | m/z 564, 566 (M + 1)$^+$ | DMSO-d6: 1.26(t, 3H, J=7.56 Hz), 1.40-1.50(m, 2H), 1.56-1.64(m, 4H), 1.67-1.82(m, 2H), 1.88-1.97 2.73(m, 2H), 3.51(dq, 2H, J=7.56, 1.52 Hz), 3.62-3.69(m, 2H), 3.86(s, 3H), 6.10-6.15(m, 1H), 6.49 (dd, 1H, J=8.56, 2.52 Hz), 6.55(d, 1H, J=2.52 Hz), 7.05-7.10(m, 1H), 7.23(s, 1H), 7.43-7.50(m, 2H) 8.05-8.11(m, 1H), 8.07(s, 1H), 8.65-8.69(m, 1H), 10.91(s, 1 |

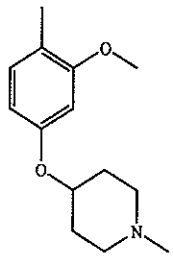
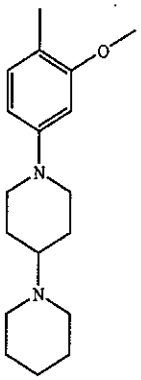
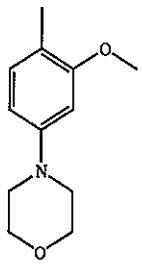
-continued



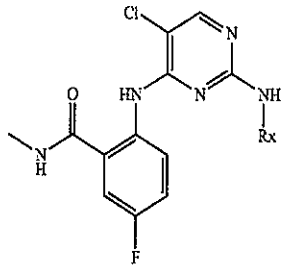
| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 9-4 |  | 0.39 (MeOH: $CH_2Cl_2$ = 1:4) | DMSO-d6: 1.19(t, 3H), 1.52-1.68(m, 2H), 1.71-1.79 (m, 4H), 1.92-2.05(m, 2H), 2.12-2.23(m, 1H), 2.76-2.85(m, 2H), 3.65-3.73(m, 2H), 3.82(s, 3H), 6.54 (dd, 1H), 6.69(d, 1H), 7.13(m, 1H), 7.45(d, 1H), 7.79 (dd, 1H), 8.15(s, 1H), 8.15-8.18(m, 1H), 8.60-8.68 (m, 1H), 8.74-8.83(m, 1H). |
| 9-5 |  | Rf (Hexane: AcOEt = 1:2): 0.30 | CDCl3: 1.27(t, 3H), 3.08-3.14(m, 4H), 3.52(q, 2H), 3.71-3.90(m, 7H), 6.05-6.18(m, 1H), 6.47(dd, 1H), 6.53(dd, 1H), 7.08(dd, 1H), 7.41-7.53(m, 2H), 8.08 (s, 1H), 8.12(d, 1H), 8.67(d, 1H), 10.94(s, 1H). |
| 9-6 |  | Rf (AcOEt:MeOH = 4:1) 0.050 | DMSO: 1.11(t, 3H), 1.60-1.69(m, 1H), 1.88-1.96(m, 2H), 2.19(s, 3H), 2.55-2.68(m, 2H), 3.30–3.45(m, 2H), 3.75(s, 3H), 4.33-4.43(m, 1H), 6.54(dd, 1H), 6.65(d, 1H), 7.07(dd, 1H), 7.30(dd, 1H), 7.43(d, 1H), 7.71(dd, 1H), 8.11(s, 1H), 8.20(s, 1H), 8.54 (br.d, 1H), 8.75(dd, 1H), 11.49(s, 1H). |
| 9-7 |  | Rf (AcOEt:MeOH = 4:1) 0.050 | CDCl3: 1.34(t, 3H), 1.62-1.68(m, 2H), 1.93-2.18(m, 8H), 2.37-2.40(br, 2H), 2.74–2.86(br, 3H), 3.20-3.23 (m, 2H), 3.34(br, 2H), 3.53(q, 2H), 3.85(s, 3H), 6.47 (dd, 1H), 6.76(d, 1H), 7.04-7.08(m, 1H), 7.30(dd, 1H), 7.53(s, 1H), 8.00(d, 1H), 8.13-8.17(m, 1H), 8.22(d, 1H), 8.42-8.53(br, 1H), 10.91(s, 1H), 11.59-11.75(br, 1H) |

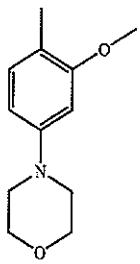
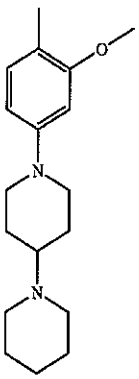
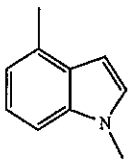
The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-6,N-dimethyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-6,N-dimethyl-benzamide and the corresponding aniline following the procedure of Example 7A



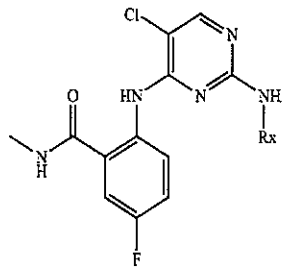

| Expl No. | Rx | Identification |
|---|---|---|
| 10-1 |  | NMR (400 MHz, DMSO-d6, δ): 1.58-1.68(m, 2H), 1.87-1.96(m, 2H), 2.13-2.22(m, 2H), 2.18(s, 3H), 2.18(s, 3H), 2.29(s, 3H), 2.57-2.65(m, 2H), 2.76(d, 3H), 3.75(s, 3H), 4.29-4.37(m, 1H), 6.45(dd, 1H), 6.61(d, 1H), 6.98(d, 1H), 7.18(dd, 1H), 7.47(d, 1H), 7.89(d, 1H), 8.02(s, 1H), 8.07(s, 1H), 8.37-8.43(m, 1H), 8.49(s, 1H). Rf: 0.39 (MeOH: $CH_2Cl_2$ = 1:4). |
| 10-2 |  | NMR (400 MHz, DMSO-d6, δ): 1.35-1.42(m, 2H), 1.45-1.60(m, 6H), 1.75-1.85(m, 2H), 2.29(s, 3H), 2.30-2.35(m, 1H), 2.43-2.50 (m, 4H), 2.57-2.66(m, 2H), 2.76(d, 3H, J=5.0 Hz), 3.65-3.74(m, 2H), 3.76(s, 3H), 6.40(dd, 1H, J=9.0, 2.0 Hz), 6.59 (d, 1H, J= 2.0 Hz), 6.98(d, 1H, J=7.6 Hz), 7.20 (dd, 1H, J=7.6, 7.6 Hz), 7.43 (d, 1H, J=9.0 Hz), 7.91-7.94(m, 1H), 7.93(s, 1H), 8.06 (s, 1H), 8.36-8.42(m, 1H) 8.47(s, 1H). MS (ESI) m/z 564, 566 $(M + 1)^+$ |
| 10-3 |  | DMSO-d6: 2.29(s, 3H), 2.77(d, 3H), 3.07-3.11(m, 4H), 3.73-3.76(m, 4H), 3.77(s, 3H), 6.41(dd, 1H), 6.63(d, 1H), 7.00(d, 1H), 7.21(dd, 1H), 7.49(d, 1H), 7.93(d, 1H), 7.96(s, 1H), 8.07(s, 1H), 8.37-8.42(m, 1H), 8.49(s, 1H). MS m/z 483 $[M + 1]^+$ |

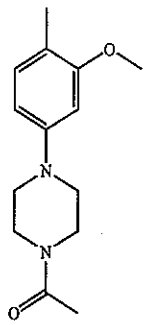
The following 2-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-5-fluoro-N-methyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-5-fluoro-N-methyl-benzamide and the corresponding aniline following the procedure of Example 7A




| Expl No. | Rx | Identification |
|---|---|---|
| 11-1 |  | NMR (400 MHz, DMSO-$d_6$, δ): 2.79(d, 3H), 3.10-3.15(m, 4H), 3.74-3.78(m, 7H), 6.50(dd, 1H), 6.66(d, 1H), 7.13-7.20 (m, 1H), 7.41(d, 1H), 7.57(dd, 1H), 8.09(s, 1H), 8.14(s, 1H), 8.55-8.65(m, 1H), 8.75-8.82(m, 1H), 11.39(s, 1H). MS (ESI): m/z 487, 489 (M + 1). |
| 11-2 |  | NMR (400 MHz, DMSO-$d_6$, δ): 1.68-1.33 (m, 8H), 1.93-1.73 (m, 2H), 2.35-2.60 (m, 1H), 2.62-2.74 (m, 2H), 2.67 (t, 2H), 2.74 (d, 3H), 3.25-3.38 (m, 4H), 3.76 (s, 3H), 3.83-3.71 (m, 2H), 6.48 (dd, 1H), 6.49 (dd, 1H), 6.63 (d, 1H), 7.15 (dd, 1H), 7.36 (d, 1H), 7.57 (dd, 1H), 8.09(s, 1H), 8.12(s, 1H), 8.65-8.55 (m, 1H), 8.78(d, 1H), 11.39 (s, 1H) MS (ESI): m/z 568, 570 ( + 1) |
| 11-3 |  | DMSO-d6: 2.80(d, 3H), 3.79(s, 3H), 6.64(d, 1H), 7.05-7.20(m, 3H), 7.23(d, 1H), 7.42-7.49(d, 1H), 7.57(dd, 1H), 8.20(s, 1H), 8.62-8.69(m, 1H), 8.75-8.82(m, 1H), 9.17(s, 1H), 11.43(s, 1H). MS m/z 425 [M + 1]' |

-continued



| Expl No. | Rx | Identification |
|---|---|---|
| 11-4 |  | DMSO-d6: 2.06(s, 3H), 2.79(d, 3H), 3.10-3.14(m, 2H), 3.15-3.19(m, 2H), 3.55-3.62(m, 4H), 3.77(s, 3H), 6.52(dd, 1H), 6.69(d, 1H), 7.15-7.23(m, 1H), 7.43(d, 1H), 7.58(dd, 1H), 8.10(s, 1H), 8.14(s, 1H), 8.56-8.65(m, 1H), 8.75-8.81(m, 1H), 11.39(s, 1H). MS m/z 528 $[M+1]^+$ |

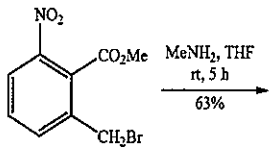
12-1 Preparation of 7-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one

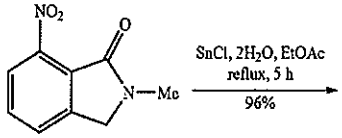
Synthetic Procedure for 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2-methyl-2,3-dihydro-isoindol-1-one

N-Methyl-7-nirto-2,3-dihydroisoindole-1-one. At room temperature, a solution of methyl 2-bromomethyl-6-nitrobenzoate (1.26 g, 4.63 mmol) in THF (13 mL) is treated with 2M soln. of methylamine in THF (14 mL), stirred for 5 h, diluted with EtOAc (100 mL), washed with sat. aqueous solution of $NaHCO_3$ (15 mL) and brine (15 mL), dried ($MgSO_4$), and evaporated. A flash chromatography (30 g of silica gel; $CH_2Cl_2$/EtOAc 1:1) gives N-Methyl-7-nirto-2,3-dihydroisoindole-1-one (0.561 g, 2.92 mmol) in 63%. Yellow solid. Rf ($CH_2Cl_2$/EtOAc 1:1) 0.46. $^1$H-NMR (400 MHz, $CDCl_3$) 3.21 (s), 4.44 (s), 7.63-7.69 (m, 2H), 7.70-7.75 (m, 1H).

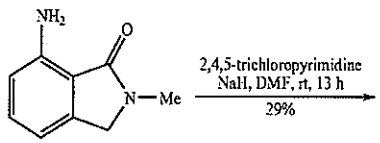
7-Amino-N-methyl-2,3-dihydroisoindole-1-one. At room temperature, a solution of N-Methyl-7-nirto-2,3-dihydroisoindole-1-one (561.0 mg, 2.92 mmol) in EtOAc (8.4 mL) is treated with $SnCl_2.2H_2O$ (2.68 g), stirred at 80° C. under reflux for 5 h, and treated with 30 mL of 5N NaOH at 0° C. After the both layers are separated, the aqueous layer is extracted with EtOAc (2×8 mL), the combined extracts are washed with brine (5 mL), dried ($MgSO_4$), and evaporated to give 7-Amino-N-methyl-2,3-dihydroisoindole-1-one (455.9 g, 2.81 mmol) in 96%. Yellow solid. $R_f$($CH_2Cl_2$/EtOAc 1:1) 0.53. $^1$H-NMR (400 MHz, $CDCl_3$) 3.12 (s), 4.28 (s), 5.20 (br. s), 6.56 (d, J=8.0), 6.68 (d, J=8.0), 7.21 (dd, J=8.0, 8.0).

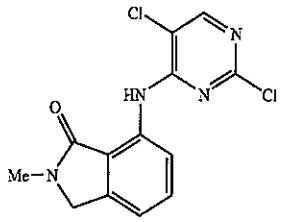
7-(4-Amino-2,5-dichloropyrimidin-4-yl)amino-N-methyl-2,3-dihydroisoindole-1-one. At 0° C., a solution of 7-Amino-N-methyl-2,3-dihydroisoindole-1-one (232.6 mg, 1.43 mmol) in DMF (2.0 mL) is treated with 60% NaH (89.8 mg), stirred at the same temperature for 1.5 h, treated with a solution of 2,4,5-trichloropyrimidine (0.557 g) in DMF (3.5 mL), stirred for 1 h, and warmed to room temperature. After furthermore stirring for 13 h, the mixture is treated with sat. aqueous $NH_4Cl$ (6 mL), and the resulting brown precipitates are collected by a filtration, followed by washing with $H_2O$, hexane, and $CH_3CN$ to give 7-(4-Amino-2,5-dichloropyrimidin-4-yl)amino-N-methyl-2,3-dihydroisoindole-1-one (130.2 g, 0.416 mmol) in 26%. Brown solid. $R_f$ ($CH_2Cl_2$/EtOAc1:1) 0.50. $^1$H-NMR (400 MHz, $CDCl_3$): 3.22 (s), 4.43 (s), 7.15 (d, J=8.0), 7.59 (dd, J=8.0, 8.0), 8.24 (s), 8.71 (d, J=8.0), 11.05 (br. s).



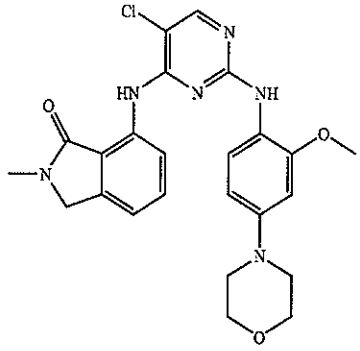
-continued



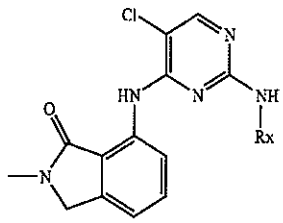

The following 7-[5-Chloro-2-(substituted phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one are prepared from 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2-methyl-2,3-dihydro-isoindol-1-one and the corresponding aniline following the procedure of Example 7A.

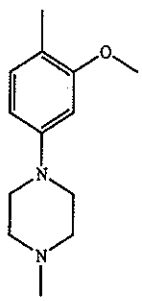
7-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-2-methyl-2,3-dihydro-isoindol-1-one



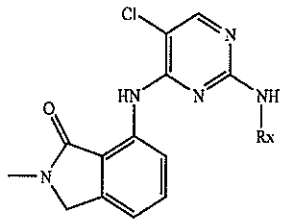

$^1$H-NMR (400 MHz, DMSO-d6, δ): 3.07 (s, 3H), 3.13-3.17 (m, 4H), 3.75 (s, 3H), 3.34-3.78 (m, 4H), 4.46 (s, 2H), 6.54 (dd, 1H, J=8.6, 2.5 Hz), 6.67 (d, 1H, J=2.5 Hz), 7.15 (d, 1H, J=7.6 Hz), 7.25-7.34 (m, 1H) 7.36 (d, 1H, J=8.6 Hz), 8.13 (s, 1H), 8.36 (s, 1H), 8.37-8.50 (m, 1H) 10.57 (s, 1H). MS (ESI) m/z 481. 483 $(M+1)^+$

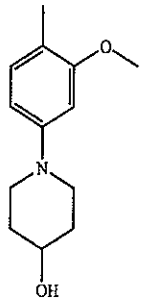
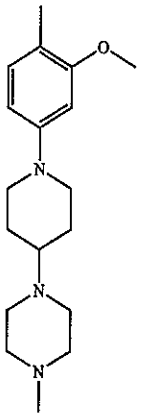
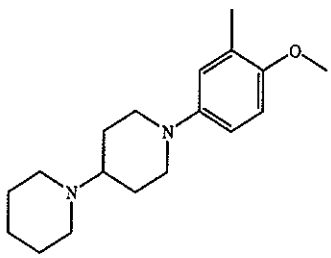
The following 7-(5-Chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino)-2-methyl-2,3-dihydro-isoindol-1-ones are prepared from 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2-methyl-2,3-dihydro-isoindol-1-one and the corresponding aniline following the procedure of Example 2:



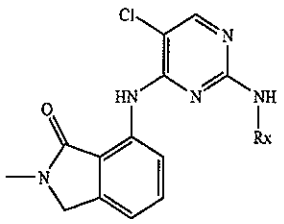

| Expl No. | Rx | Mass(m/z) | NMR (400 MHz) δ (ppm) |
|---|---|---|---|
| 12-2 |  | 494 $[M+1]^+$ | DMSO-d6: 2.24(s, 3H), 2.45-2.50(m, 4H), 3.07(s, 3H), 3.15-3.19(m, 4H), 3.74(s, 3H), 4.46(s, 2H), 6.52(dd, 1H), 6.66(d, 1H), 7.15 (d, 1H), 7.25-7.36(m, 2H), 8.12(s, 1H), 8.35(s, 1H), 8.35-8.45(m, 1H), 10.57(s, 1H) |

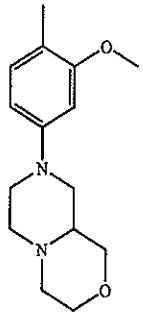
-continued



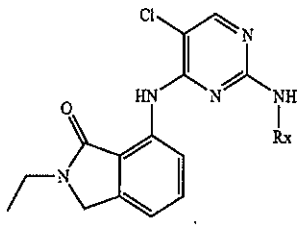
| Expl No. | Rx | Mass(m/z) | NMR (400 MHz) δ (ppm) |
|---|---|---|---|
| 12-3 |  | 495 $[M+1]^+$ | DMSO-d6: 1.48-1.57(m, 2H), 1.83-1.88(m, 2H), 2.83-2.90(m, 2H), 3.07(s, 3H), 3.51-3.60(m, 2H), 3.61-3.70(m, 2H), 3.73(s, 3H), 4.46(s, 2H), 4.69(d, 1H), 6.52(dd, 1H), 6.64(d, 1H), 7.14 (d, 1H), 7.25-7.35(m, 2H), 8.12(s, 1H), 8.33(s, 1H), 8.35-8.45(m, 1H), 10.57(s, 1H) |
| 12-4 |  | 577 $[M+1]^+$ | DMSO-d6: 1.48-1 .59(m, 2H), 1.83-1.88(m, 2H), 2.14(s, 3H), 2.25-2.39(m, 4H), 2.42-2.60(m, 5H), 2.66-2.73(m, 2H), 3.07(s, 3H), 3.73-3.77(m, 2H), 3.74(s, 3H), 4.46(s, 2H), 6.52(dd, 1H), 6.64(d, 1H), 7.14 (d, 1H), 7.25-7.34(m, 2H), 8.12(s, 1H), 8.34(s, 1H), 8.35-8.45(m, 1H), 10.57(s, 1) |
| 12-5 |  | 562 $[M+1]^+$ | DMSO-d6: 1.35-1.65(m, 8H), 1.73-1.85(m, 2H), 2.40-2.59(m, 7H), 3.08(s, 3H), 3.52-3.61(m,2H), 3.73(s, 3H), 4.47(s, 2H), 6.72(dd, 1H), 6.94(d, 1H), 7.17(d, 1H), 7.34-7.39(m, 2H), 8.21(s, 1H), 8.37(s, 1H), 8.45-8.53(m, 1H), 10.64(s, 1H) |

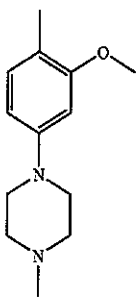
-continued



| Expl No. | Rx | Mass(m/z) | NMR (400 MHz) δ (ppm) |
|---|---|---|---|
| 12-6 |  | MS m/z 536 | DMSO-$d_6$: 2.19-2.42 (m, 4H), 2.65-2.89 (m, 3H), 3.07 (s, 3H), 3.11-3.30 (m, 1H), 3.48-3.61 (m, 2H), 3.62-3.71 (m, 1H), 3.75 (s, 3H), 3.75-3.83 (m, 2H), 4.47 (s, 2H), 6.48-6.52 (m, 1H), 6.66 (d, 1H), 7.15 (d, 1H), 7.26-7.37 (m, 2H), 8.13 (s, 1H), 8.35 (s, 1H), 8.42 (brs, 1H), 10.57 (s, 1H). |

The following 7-(5-Chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino)-2-ethyl-2,3-dihydroisoindol-1-ones are prepared from 7-(2,5-Dichloro-pyrimidin-4-ylamino)-2-ethyl-2,3-dihydro-isoindol-1-one and the corresponding aniline following the procedure of Example 2:



| Expl No. | Rx | Mass(m/z) | NMR (400 MHz) δ (ppm) |
|---|---|---|---|
| 13-1 |  | 508 $[M + 1]^+$ | DMSO-d6: 1.19(t, 3H), 2.24(s, 3H), 2.47-2.51(m, 4H), 3.15-3.21(m, 4H), 3.54(q, 2H), 3.74(s, 3H), 4.48(s, 2H), 6.54(dd, 1H), 6.65(d, 1H), 7.15 (d, 1H), 7.26-7.36(m, 2H), 8.12(s, 1H), 8.34(s, 1H), 8.37-8.48(m, 1H), 10.58(s, 1H) |

Example 7B

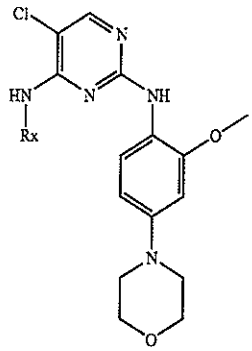
2-[5-Chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide (Alternative Synthesis to Example 7A)

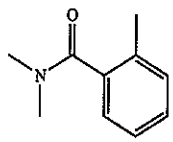
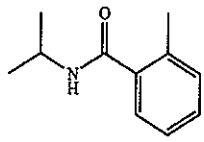
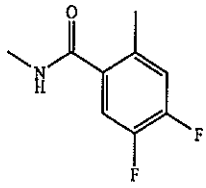
To a suspension of 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin ylamino]-benzoic acid (5.5 g, 12.1 mmol) in 100 mL of THF are added $Et_3N$ (2.06 mL, 14.8 mmol) and isobutyl chloroformate (1.7 mL, 12.8 mmol) at −5° C. After stirring at the same temperature for 30 min, the reaction mixture is further stirred at room temperature for 1 hour and then $H_2O$ is added to the reaction mixture. The resulting precipitate is collected by filtration, washed with $H_2O$, and dried under reduced pressure to give an intermediate (4.80 g) (10.96 mmol, 91%) as yellow solid.

NMR (400 MHz, DMSO-d6, δ): 3.10-3.20 (m, 4H), 3.70-3.80 (m, 4H), 3.93 (s, 3H), 6.53 (dd, 1H, J=9.08, 2.0 Hz), 6.70 (d, 1H, J=2.0 Hz), 7.49-7.54 (m, 1H), 7.67 (d, 1H, J=8.56 Hz), 7.89 (s, 1H), 7.85-7.95 (m, 1H), 8.23 (d, 1H, J=9.08 Hz), 8.26 (d, 1H, J=8.56 Hz), 12.60 (s, 1H).

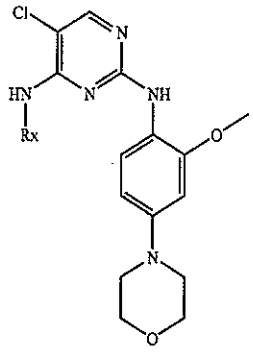
To a 1M solution of methylamine in THF (560 μl, 0.56 mmol) is added 82 mg of the obtained intermediate (0.187 mmol) followed by 1M solution of NaHMDS in THF (560 μl, 0.56 mmol) dropwise. After the reaction mixture is stirred for 10 minutes, 5 mL of $H_2O$ is added and extraction is performed with AcOEt. The organic layer is washed with brine, dried over $Na_2SO_4$, concentrated under reduced pressure, and purified by silica gel column chromatography (Hexane: AcOEt=1:1 to AcOEt) to give the title compound as a pale yellow solid. Data are given in Example 7A.

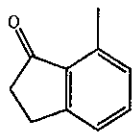
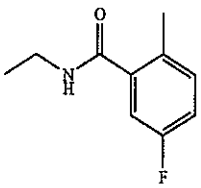
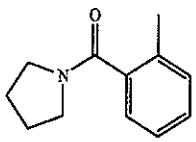
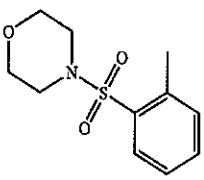
By repeating the procedures described above using appropriate starting materials and conditions the following compounds are obtained as identified below.



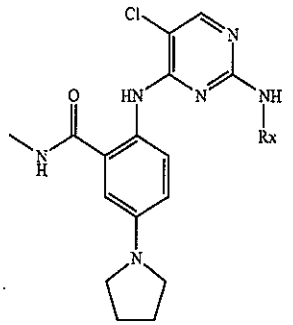

| Expl No. | Ry | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 14-1 |  | 0.10 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 3.02-3.19 (m, 10H), 3.83-3.91 (m, 4H), 3.87 (s, 3H), 6.45 (dd, 1H), 6.52 (d, 1H), 7.09-7.14 (m, 1H), 7.29 (m, 1H), 7.31 (dd, 1H), 7.38-7.45 Cm, 1H), 8.06 (s, 1H), 8.14 (d, 1H), 8.39 (d, 1H), 8.97 (s, 1H). |
| 14-2 |  | 0.36 (n-hexane: AcOEt = 1:2) | $CDCl_3$: 1.27 (d, 6H), 3.09-3.16 (m, 4H), 3.81-3.92 (m, 4H), 3.89 (s, 3H), 4.26-4.37 (m, 1H), 5.93-5.98 (m, 1H), 6.48 (dd, 1H), 6.53 (d, 1H), 7.05-7.11 (m, 1H), 7.42-7.49 (m, 2H), 8.08 (s, 1H), 8.12 (d, 1H), 8.65 (d, 1H), 10.88 (br.s, 1H). |
| 14-3 |  | 505 $[M + 1]^+$ | DMSO-d6: 2.79(d, 3H), 3.09-3.14(m, 4H), 3.74-3.77(m, 4H), 3.75(s, 3H), 6.49(dd, 1H), 6.65(d, 1H), 7.30 (d, 1H), 7.84(dd, 1H), 8.12(s, 1H), 8.40(s, 1H), 8.65-8.79(m, 2H), 11.39(s, 1H) |

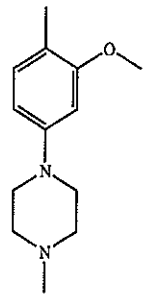
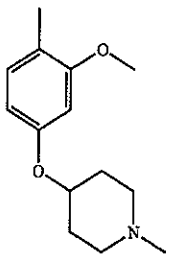
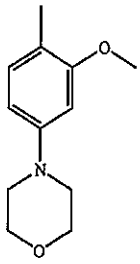
-continued



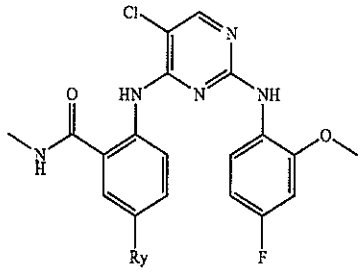
| Expl No. | Ry | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 14-4 |  | 466 $[M+1]^+$ | DMSO-d6: 2.70-2.75(m, 2H), 3.04-3.09(m, 2H), 3.12-3.18(m, 4H), 3.74-3.80(m, 4H), 3.75(s, 3H), 6.54(dd, 1H), 6.67(d, 1H), 7.14 (d, 1H), 7.34(d, 1H),7.37-7.44(m, 1H), 8.17(s, 1H), 8.35-8.50(m, 1H), 8.44(s, 1H), 10.59(s, 1H) |
| 14-5 |  | Rf (Hexane: AcOEt = 1:2): 0.31 | DMSO: 1.18 (t, 3H), 3.11-3.21 (4, 4H), 3.30-3.60 (m, 2H), 3.71-3.85 (m, 7H), 6.50-6.58 (m, 1H), 6.71 (d, 1H), 7.17-7.26 (m, 1H), 7.46 (d, 1H), 7.64 (dd, 1H), 8.14 (s, 1H), 8.19 (s, 1H), 8.57-8.68 (m, 1H), 8.80-8.87(m, 1H), 11.36 (s, 1H). |
| 14-6 |  | Rf (Hexane: AcOEt = 1:1): 0.051 | DMSO: 1.71-1.92 (m, 2H), 1.92-2.06 (m, 2H), 3.08-3.14 (m, 4H), 3.48-3.57 (m, 2H), 3.63-3.75 (m, 2H), 3.84-3.90 (m, 7H), 6.47 (dd, 1H), 6.53 (d, 1H), 7.09 (ddd, 1H), 7.25-7.29 (m, 1H), 7.38-7.44 (m, 1H), 8.06 (s, 1H), 8.15 (d, 1H), 8.45 (dd, 1H), 9.60 (s, 1H). |
| 14-7 |  | | $^1$H-NMR (400 MHz, δ ppm, $CDCl_3$): 3.04-3.10 (m, 4H), 3.10-3.16 (m, 4H), 3.63-3.68 (m, 4H), 3.85-3.90 (m, 7H), 6.46 (dd, 1H), 6.53 (d, 1H), 7.20-7.25 (m, 1H), 7.33 (brs, 1H), 7.56-7.62 (m, 1H), 7.85 (dd, 1H), 8.03 (d, 1H), 8.12 (s, 1H), 8.57-8.61 (m, 1H), 9.30 (s, 1H). |

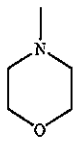
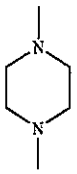
The following 2-(5-Chloro-2-(subst. phenylamino)-pyrimidin-4-ylamino)-N-methyl-5-pyrrolidin-1-yl benzamides are prepared from 2-(5-Chloro-2-methyl-pyrimidin-4-ylamino)-N-methyl-5-pyrrolidin-1-yl-benzamide and the corresponding aniline following the procedure of Example 2:



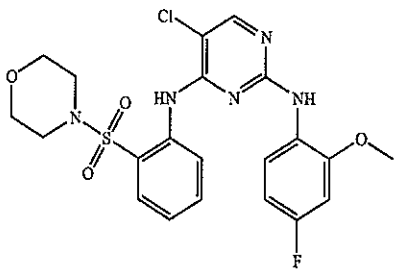
| Expl No. | Rx | Mass(m/z) | NMR (400 MHz) δ (ppm) |
|---|---|---|---|
| 15-1 |  | 551 [M + 1]+ | DMSO-d6: 1.94-1.99(m, 4H), 2.23(s, 3H), 2.43-2.48(m, 4H), 2.78(d, 3H), 3.11-3.17(m, 4H), 3.22-3.29(m, 4H), 3.76(s, 3H), 6.46(dd, 1H), 6.48-6.53(m, 1H), 6.63(d, 1H), 6.79(d, 1H), 7.44(d, 1H), 7.89(s, 1H), 7.99(s, 1H), 8.24(d, 1H), 8.60(d, 1H), 10.88(s, 1H) |
| 15-2 |  | 566 [M + 1]+ | DMSO-d6: 1.60-1.70(m, 2H), 1.90-2.00(m, 6H), 2.12-2.20(m, 2H), 2.18(s, 3H), 2.60-2.65(m, 2H), 2.78(d, 3H), 3.22-3.28(m, 4H), 3.75(s, 3H), 4.25-4.37(m, 1H), 6.49-6.55(m, 2H), 6.62(d, 1H), 6.80(d, 1H), 7.53(d, 1H), 7.90(s, 1H), 8.00(s, 1H), 8.24(d, 1H), 8.58-8.63(m, 1H), 10.88(s, 1H) |
| 15-3 |  | 538 [M + 1]+ | DMSO-d6: 1.94-1.99(m, 4H), 2.78(d, 3H), 3.09-3.15(m, 4H), 3.22-3.27(m, 4H), 3.73-3.77(m, 4H), 3.76(s, 3H), 6.47(dd, 1H), 6.47-6.53(m, 1H), 6.65(d, 1H), 6.79(d, 1H), 7.47(d, 1H), 7.90(s, 1H), 7.99(s, 1H), 8.24(d, 1H), 8.60(d, 1H), 10.88(s, 1H) |

The following 2-[5-Chloro-2-(4-fluoro-2-methoxy-phenylamino)-pyrimidin-4-ylamino]-5-subst.-N-methyl-benzamide are prepared from the corresponding aniline following the procedure of Example 2:



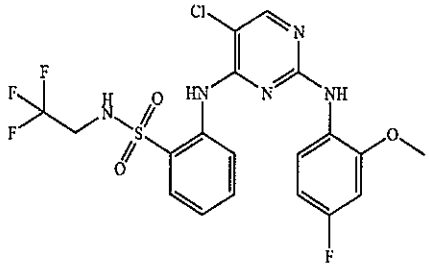

| Expl No. | Ry | Mass(m/z) | NMR (400 MHz) δ (ppm) |
|---|---|---|---|
| 16-1 |  | 487 $[M+1]^+$ | DMSO-d6: 2.79(d, 3H), 3.11-3.15(m, 4H), 3.74-3.81(m, 4H), 3.81(s, 3H), 6.76(ddd, 1H), 6.95-7.05(m, 2H), 7.21(d, 1H), 7.72(dd, 1H), 8.08(s, 1H), 8.09(s, 1H), 8.33(d, 1H), 8.63-8.73(m, 1H), 11.17(s, 1H) |
| 16-2 |  | 500 $[M+1]^+$ | DMSO-d6: 2.24(s, 3H), 2.45-2.52(m, 4H),2.79(d, 3H), 3.13-3.18(m, 4H), 3.81(s, 3H), 6.75(ddd, 1H), 6.94-7.02(m, 2H), 7.20(d, 1H), 7.73(dd, 1H), 8.03-8.11(m, 2H), 8.30(d, 1H), 8.60-8.70(m, 1H), 11.14(s, 1H) |
| 16-3 |  | 432 $[M+1]^+$ | DMSO-d6: 2.79(d, 3H), 3.80-3.81(m, 6H), 6.75(ddd, 1H), 6.90-7.02(m, 2H), 7.27(d, 1H), 7.67(dd, 1H), 8.10(s, 1H), 8.16(s, 1H), 8.39(d, 1H), 8.70-8.76(m, 1H), 11.20(s, 1H) |
| 16-4 |  | 568 $[M+1]^+$ | DMSO-d6: 1.35-1.62(m, 8H), 1.78-1.85(m, 2H), 2.30-2.40(m, 1H), 2.41-2.52(m, 4H), 2.60-2.70(m, 2H), 2.78(d, 3H), 3.70-3.80(m, 2H), 3.81(s, 3H), 6.75(ddd, 1H), 6.95-7.02(m, 2H), 7.20(d, 1H), 7.72(dd, 1H), 8.05-8.08(m, 2H), 8.28(d, 1H), 8.63-8.69(m, 1H), 11.12(s, 1H) |

Example 16B



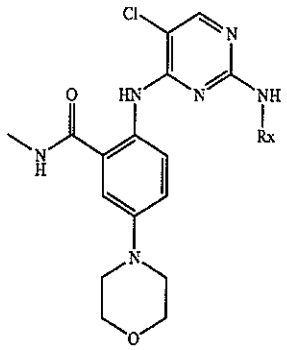
$CDCl_3$: 3.01-3.10 (m, 4H), 3.63-3.68 (m, 4H), 3.89 (s, 3H), 6.59 (ddd, 1H), 6.66 (dd, 1H), 7.20-7.26 (m, 1H), 7.36 (s, 1H), 7.57-7.63 (m, 1H), 7.84 (dd, 1H), 8.09-8.14 (m, 1H), 8.14 (s, 1H), 8.53 (d, 1H), 9.30 (s, 1H).

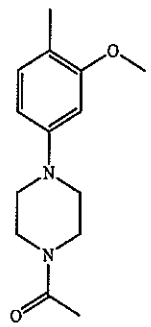
Example 16C



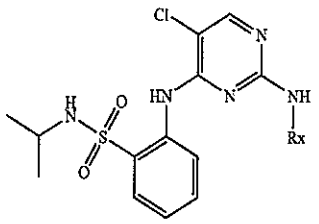
$CDCl_3$: 3.56-3.65 (m, 2H), 3.88 (s, 3H), 5.11-5.19 (m, 1H), 6.50-6.56 (m, 1H), 6.61-6.66 (m, 1H), 7.25-7.29 (m, 1H), 7.38 (brs, 1H), 7.58-7.62 (m, 1H), 7.97 (dd, 1H), 8.02-8.10 (m, 1H), 8.15 (s, 1H), 8.41 (dd, 1H), 8.81 (s, 1H).

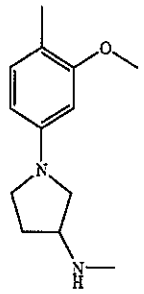
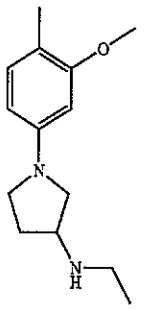
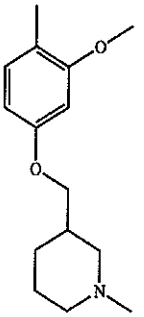
The following 2-(5-Chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino)-5-fluoro-N-methyl-benzamide are prepared from 2-(2,5-Dichloro-pyrimidin-4-ylamino)-5-fluoro-N-methyl-benzamide and the corresponding aniline following the procedure of Example 2:



| Expl No. | Rx | Mass(m/z) | NMR (400 MHz) δ (ppm) |
|---|---|---|---|
| 18-1 |  | 595 $[M+1]^+$ | DMSO-d6: 2.06 (s, 3H), 2.78 (d, 3H), 3.05-3.18 (m, 8H), 3.53-3.64 (m, 4H), 3.68-3.77 (m, 4H), 3.77 (s, 3H), 6.51 (dd, 1H), 6.69 (d, 1H), 6.88 (br.d, 1H), 7.20 (d, 1H), 7.43 (d, 1H), 7.99-8.03 (m, 2H), 8.34 (br.d, 1H), 8.63-8.71 (m, 1H), 11.15 (s, 1H). |

The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-isopropyl-benzenesulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-isopropyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A



| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-1 |  | 0.39 (MeOH: $CH_2Cl_2$ = 1:4) | DMSO-d6: 0.94(d, 6H), 1.75-1.84(m, 1H), 2.07-2.16(m, 1H), 2.33(s, 3H), 2.98-3.04(m, 1H), 3.22-3.36(m, 5H), 3.42-3.47(m, 1H), 3.74(s, 3H), 6.05(dd, 1H), 6.18(d, 1H), 7.18(dd, 1H), 7.25(d, 1H), 7.35-7.45(m, 1H), 7.77-7.82(m, 1H), 7.70-8.10(m, 1H), 8.09-8.17 (m, 2H), 8.45-8.63(m, 1H), 9.34(s, 1H) |
| 19-2 |  | 0.40 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 1.00(d, 6H), 1.13(t, 3H), 1.83-1.92(m, 1H), 2.23-2.30(m, 1H), 2.70-2.78(m, 2H), 3.08-3.13(m, 1H), 3.27-3.54 (m, 5H), 3.85(s, 3H), 4.33(d, 1H), 6.05(d, 1H), 6.13(s, 1H), 7.13(bs, 1H), 7.18-7.22(m, 1H), 7.52-7.56(m, 1H), 7.83-7.86(m, 1H), 7.95-7.98(m, 1H), 8.09(s, 1H), 8.47-8.49(m, 1H), 8.89(s, 1H) |
| 19-3 |  | 0.30 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 0.93 (d, 6H), 1.05-1.09(m, 1H), 1.48-1.99(m, 6H), 2.16(s,3H), 2.61-2.67(m, 1H), 2.80-2.83(m, 1H), 3.75(s, 3H), 3.80-3.89(m, 2H), 6.44-6.47(m, 1H), 6.62-6.63(m, 1H), 7.18-7.22(m, 1H), 7.42-7.46(m, 1H), 7.80-7.89(m, 2H), 8.17(s, 1H), 8.23(s, 1H), 8.42-8.44(m, 1H), 8.89(s, 1H) |

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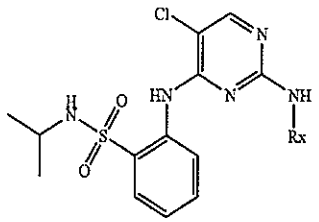
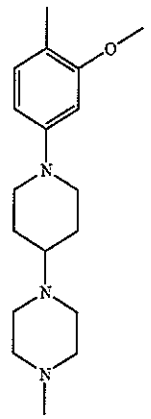
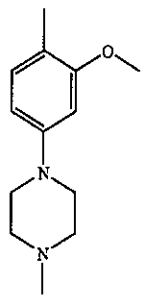
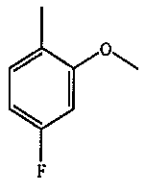
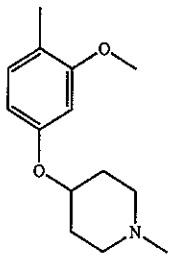


| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-4 |  | 0.69 (MeOH: $CH_2Cl_2$ = 1:3) | DMSO-d6: 0.94(d, 6H), 1.45-1.57(m, 2H), 1.80-1.88(m, 2H), 2.14(s, 3H), 2.25-2.35(m, 4H), 2.45-2.55(m, 4H), 2.62-2.70(m, 2H), 3.28-3.37(m, 1H), 3.68-3.74(m, 2H), 3.75(s, 3H), 6.44(dd, 1H, J=8.82, 2.0 Hz), 6.61(d, 1H, J=2.0 Hz), 7.21(dd, 1H), 7.37(d, 1H), 7.45(dd, 1H), 7.81 (dd, 1H, J=1.82, 1.52 Hz), 7.84-7.92(m, 1H), 8.12-8.20(m, 1H), 8.16(s, 1H), 8.43-8.51(m, 1H), 9.31(s, 1H) |
| 19-5 |  | 0.35 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 0.93(d, 6H), 2.23(s, 3H), 2.45-2.48(m, 4H), 3.12-3.15(m,4H), 3.75(s, 3H), 6.42-6.45(m, 1H), 6.63 (s, 1H), 7.19-7.23(m, 1H), 7.38-7.47(m, 2H), 7.80-7.89(m, 2H), 8.16(s, 1H), 8.46-8.48(m, 1H), 9.34(s, 1H) |
| 19-6 |  | 0.45 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 0.99(d, 6H), 3.40-3.49(m, 1H), 3.88(s, 3H), 4.29-4.31(d, 1H), 6.51-6.56(m, 1H), 6.62-6.65 (m, 1H), 7.24-7.28(m, 1H), 7.37(s, 1H), 7.56-7.60(m, 1H), 7.98-8.15(m, 3H), 8.34-8.37(m, 1H), 8.89(s, 1H) |
| 19-7 |  | 0.28 (n-hexane: AcOEt = 1:1) | DMSO-d6: 0.93(d, 6H), 1.59-1.67(m, 2H), 1.90-1.93(m, 2H), 2.10-2.24(m, 5H), 2.60-2.67(m, 2H), 3.74(s, 3H), 4.33-4.37(m, 1H), 6.47-6.50(m, 1H), 6.63(d, 1H), 7.18-7.22(m, 1H), 7.41-7.45(m, 2H), 7.79-7.87(m, 2H), 8.16(s, 1H), 8.21(s, 1H), 8.41-8.43(m, 1H), 9.29(s, 1H) |

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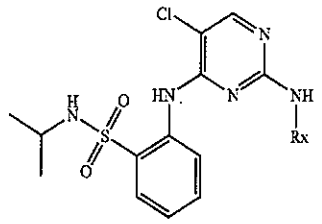
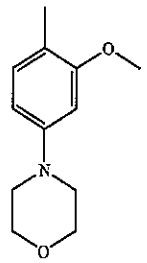
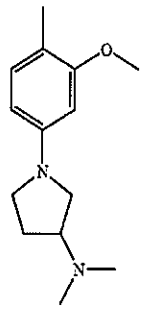
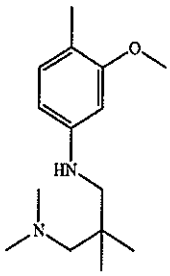
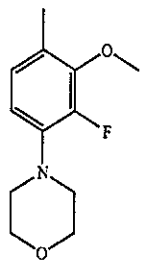


| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-8 |  | 0.25 (n-hexane: AcOEt = 1:1) | DMSO-d6: 0.93(d, 6H), 3.09-3.12(m, 4H), 3.74-3.76(m, 7H), 6.43-6.46(m, 1H), 6.64(s, 1H), 7.19-7.23(m, 1H), 7.41-7.48(m, 2H), 7.80(d, 1H), 7.82(d, 1H), 8.17(s, 1H), 8.46-8.48(m, 1H), 9.31(s, 1H) |
| 19-9 |  | 0.56 (MeOH: $CH_2Cl_2$ = 1:4) | DMSO-d6: 0.93(d, 6H), 1.89-1.90(m, 1H), 2.30(bs, 6H), 3.13-3.50(m, 6H), 3.74(s, 3H), 6.10(d, 1H), 6.22(s, 1H), 7.16-7.20(m, 1H), 7.25-7.27(m, 1H), 7.40(bs, 1H), 7.79-7.81(m, 1H), 7.86-7.88(m, 1H), 8.12(s, 1H), 8.15(s, 1H), 8.51(s, 1H), 9.34(s, 1H) |
| 19-10 |  | 0.45 (MeOH: $CH_2Cl_2$ = 1:4) | $CDCl_3$: 0.99(d, 12H), 2.27(s, 2H), 2.31(s, 6H), 2.96(s, 2H), 3.39-3.48(m, 1H), 3.83(s, 3H), 4.30(d, 1H), 6.09-6.12(m, 1H), 6.19(d, 1H), 7.11(s, 1H), 7.19-7.23(m, 1H), 7.51-7.57(m, 1H), 7.76-7.79(m, 1H), 7.95(d, 1H), 8.09(s, 1H), 8.46-8.49(m, 1H), 8.88(s, 1H) |
| 19-11 |  | 0.30 (n-hexane: AcOEt = 1:1) | DMSO-d6: 0.93(d, 6H), 2.96-2.99(m, 4H), 3.74-3.76(m, 7H), 6.67-6.72(m, 1H), 7.21-7.25(m, 1H), 7.31-7.34(m, 1H), 7.44-7.48(m, 1H), 7.80-7.83(m, 1H), 7.88(d, 1H), 8.21(s, 1H), 8.42(d, 1H), 8.58(s, 1H), 9.30 (s, 1H) |

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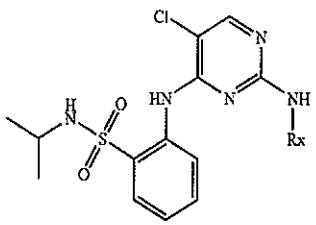
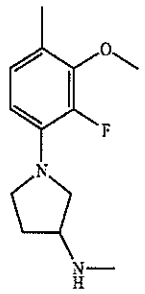
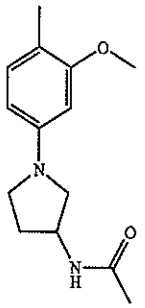
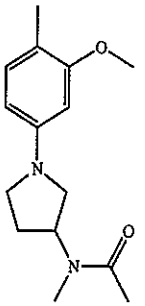
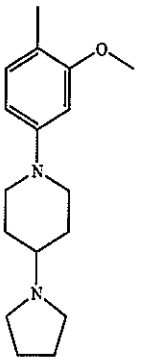


| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-12 |  | 0.42 (MeOH: $CH_2Cl_2$ = 1:4) | DMSO-d6: 0.94(d, 6H), 1.68-1.76(m, 1H), 1.99-2.07(m, 1H), 2.29(s, 3H), 3.05-3.49(m, 6H), 3.75(s, 3H), 6.36-6.40(m, 1H), 7.10-7.37(m, 3H), 7.70-7.80(m, 1H), 8.08-8.39(m, 3H), 9.24(s, 1H) |
| 19-13 |  | 0.50 (MeOH: $CH_2Cl_2$ = 1:4) | $CDCl_3$: 1.01(d, 6H), 1.94-1.96(m, 1H), 2.01(s, 3H), 2.29-2.37(m, 1H), 3.19-3.58(m, 5H), 3.86(s, 3H), 4.42(d, 1H), 4.59-4.63(m, 1H), 5.70(d, 1H), 6.05-6.08(m, 1H), 6.15-6.16(m, 1H), 7.17-7.24(m, 2H), 7.53-7.57(m, 1H), 7.90(d, 1H), 7.91-7.98(m, 1H), 8.09(s, 1H), 8.47(d, 1H), 8.91(s, 1H) |
| 19-14 |  | 0.53 (MeOH: $CH_2Cl_2$ = 1:4) | $CDCl_3$: 1.00(d, 6H), 2.04(s, 3H), 2.05-2.29(m, 2H), 2.96(s, 3H), 3.19-3.54(m, 5H), 3.86(s, 3H), 4.57-4.63(m, 1H), 5.39-5.46(m, 1H), 6.07-6.09(m, 1H), 6.16(d, 1H), 7.18-7.26(m, 2H), 7.53-7.57(m, 1H), 7.89-7.98(m, 2H), 8.08(s, 1H), 8.47(d, 1H), 8.94(d, 1H) |
| 19-15 |  | 0.56 (MeOH: $CH_2Cl_2$ = 1:4) | DMSO-d6: 0.93(d, 6H), 1.48-1.56(m, 2H), 1.65-1.75(m, 4H), 1.90-1.93(m, 2H), 2.05-2.15(m, 1H), 2.45-2.55(m, 5H), 2.69-2.75(m, 2H), 3.61(d, 2H), 3.74(s, 1H), 6.42-6.51(m, 1H), 6.61(d, 1H), 7.18-7.22(m, 1H), 7.37(d, 1H), 7.43-7.47(m, 1H), 7.80(d, 1H), 7.81-7.89(m, 1H), 8.16(d, 1H), 8.46-8.48(m, 1H), 9.31(s, 1H) |

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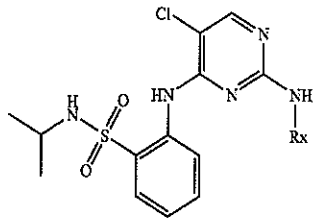
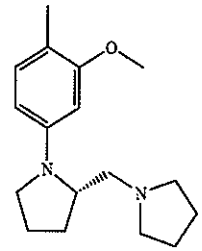
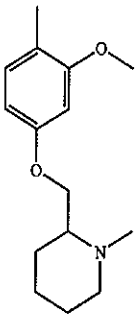
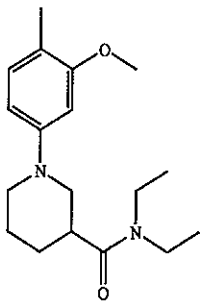
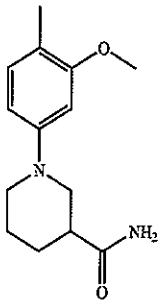


| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-16 |  | 0.56 (MeOH: $CH_2Cl_2$ = 1:4) | DMSO-d6: 0.92(d, 6H), 1.65-1.75(m, 4H), 1.88-2.00(m, 4H), 2.39-2.43(m, 2H), 2.60-2.65(m, 2H), 3.03-3.07(m, 1H), 3.03-3.40(m, 2H), 3.70(s, 3H), 3.77-3.78(m, 1H), 6.09(d, 1H), 6.23(s, 1H), 7.13-7.78(d, 1H), 7.86(d, 1H), 8.10(s, 1H), 8.13(s, 1H), 8.40-8.50(m, 1H), 9.31(s, 1H) |
| 19-17 |  | 0.23 (n-hexane: AcOEt = 1:1) | DMSO-d6: 0.93(d, 6H), 1.24.-1.57(m, 4H), 1.69-1.78(m, 2H), 1.98-2.04(m, 1H), 2.15-2.33(m, 5H), 2.70-2.80(m, 1H), 3.74(s, 3H), 3.91-3.94(m, 1H), 4.05-4.09(m, 1H), 6.46-6.49(m, 1H), 6.63(d, 1H), 7.18-7.22(m, 1H), 7.42-7.46(m, 2H), 7.80(d, 1H), 7.89(d, 1H), 8.17(s, 1H), 8.25(s, 1H), 8.42-8.44(m, 1H), 9.31(s, 1H) |
| 19-18 |  | 0.48 (n-hexane: AcOEt = 1:1) | DMSO-d6: 0.93(d, 6H), 1.03(t, 3H), 1.13(t, 3H), 1.42-1.81(m, 4H), 2.57-2.83(m, 4H), 3.17-3.41(m, 4H), 3.65-3.75(m, 1H), 3.80(s, 3H), 4.21 (bs, 1H), 6.42-6.47(m, 2H), 6.51(d, 1H), 6.63(d, 1H), 7.18-7.22(m, 1H), 7.38-7.47(m, 2H), 7.80-7.82(m, 1H), 7.89(d, 1H), 8.16(s, 1H), 8.47-8.49(m, 1H), 9.31(s, 1H) |
| 19-19 |  | 0.44 (CH2Cl2: MeOH = 9:1) | $CDCl_3$: 1.45-1.62 (m, 2H), 1.72-1.78 (m, 1H), 1.82-1.90 (m, 1H), 2.40-2.46 (m, 1H), 2.61-2.75 (m, 2H), 3.75-3.70 (m, 2H), 3.76 (s, 3H), 6.45 (dd, 1H), 6.62 (d, 1H), 6.85 (s, 1H), 7.19-7.23 (m, 1H), 7.36-7.48 (m, 3H), 7.80-7.82 (m, 1H), 7.85-7.93 (br, 1H), 8.16 (s, 2H), 8.43-8.52 (m, 1H), 9.31 (s, 1H) |

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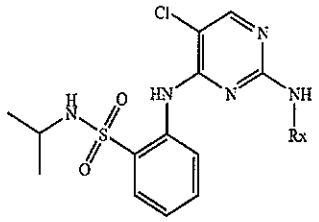
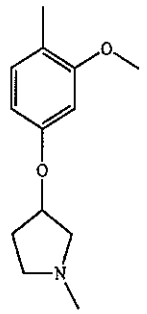
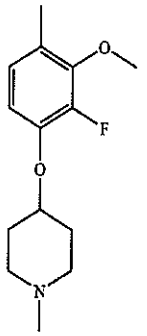
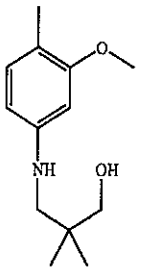
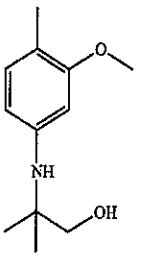


| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-20 |  | Ms: 547 | DMSO-d6: 0.94 (d, 6H), 1.73-1.82 (m, 1H), 2.23-2.33 (m, 4H), 2.34-2.41 (m, 1H), 2.54-2.62 (m, 1H), 2.62-2.69 (m, 1H), 2.77-2.82 (m, 1H), 3.25-3.35 (m, 1H), 3.74 (s, 3H), 4.85-4.92 (m, 1H), 6.4 (dd, 1H), 6.57 (d, 1H), 7.16-7.24 (m, 1H), 7.38-7.51 (m, 1H), 7.81 (d, 1H), 7.82-7.94 (m, 1H), 8.16 (s, 1H), 8.22 (brs, 1H), 8.38-8.48 (m, 1H), 9.3 (brs, 1H) |
| 19-21 |  | Ms: 579 | DMSO-d6: 0.92 (d, 6H), 1.61-1.71 (m, 2H), 1.86-1.96 (m, 2H), 2.12-2.22 (m, 5H), 2.57-2.64 (m, 2H), 3.2-3.4 (m, 1H), 3.77 (s, 3H), 4.27-4.35(m, 1H), 6.86 (dd, 1H), 7.19-7.27 (m, 1H), 7.39-7.46 (m, 1H), 7.81 (dd, 1H), 7.84-7.92 (m, 1H), 8.21 (s, 1H), 8.36-8.42 (m, 1H), 8.62 (s, 1H), 9.28 (s, 1H) |
| 19-22 |  | Ms: 549 | DMSO-d6: 0.90 (s, 6H), 0.94 (d, 6H), 2.9 (d, 2H), 3.24 (d, 2H), 3.25-3.35(m, 1H), 3.27-3.36 (m, 1H), 3.68 (s, 3H), 4.58 (t, 1H), 5.3 (t, 1H), 6.16 (dd, 1H), 6.39 (d, 1H), 7.13 (d, 1H), 7.15-7.21 (m, 1H), 7.35-7.45 (m, 1H), 7.8 (dd, 1H), 7.83-7.92 (m, 1H), 8.09 (s, 1H), 8.11 (s, 1H), 8.45-8.57 (m, 1H), 9.33 (s, 1H) |
| 19-23 |  | Rf: 0.51 (n-hexane: AcOEt = 1:1) | DMSO-d6: 0.94 (d, 6H), 1.22 (s, 6H), 3.25-3.35 (m, 1H), 3.36 (d, 2H), 3.68 (s, 3H), 4.73-4.79 (brs, 1H), 4.81 (t, 1H), 6.29 (dd, 1H), 6.44 (d, 1H), 7.14-7.22 (m, 2H), 7.38-7.46 (m, 1H), 7.8 (dd, 1H), 7.85-7.9 (m, 1H), 8.1 (s, 1H), 8.13 (s, 1H), 8.45-8.55 (m, 1H), 9.32 (s, 1H) |

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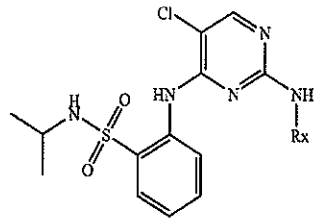
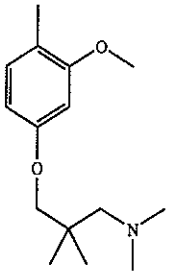
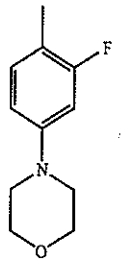
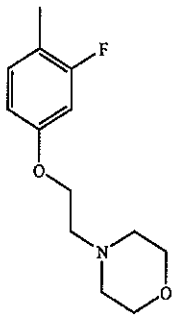
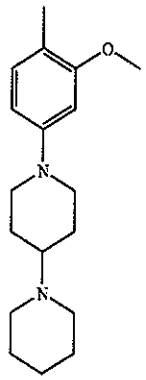


| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-24 |  | Ms: 577 | DMSO-d6: 0.93 (d, 6H), 0.96 (s, 6H), 2.22 (s, 6H), 3.25-3.35 (m, 1H), 3.7 (s, 3H), 3.75 (s, 3H), 6.46 (dd, 1H), 6.62 (d, 1H), 7.16-7.23 (m, 1H), 7.38-7.47 (m, 1H), 7.81 (dd, 1H), 7.85-7.9 (m, 1H), 8.17 (s, 1H), 8.23 (s, 1H), 8.38-8.48 (m, 1H), 9.31 (s, 1H) |
| 19-25 |  | Ms: 521 | DMSO-d6: 0.94 (d, 6H), 3.12 (t, 4H), 3.25-3.35 (m, 1H), 3.75 (t, 4H), 6.73 (dd, 1H), 6.85 (dd, 1H), 7.16-7.24 (m, 1H), 7.25-7.32 (m, 1H), 7.38-7.47 (m, 1H), 7.8 (dd, 1H), 7.88 (d, 1H), 8.18 (s, 1H), 8.42-8.52 (m, 1H), 8.86 (s, 1H), 9.36 (s, 1H) |
| 19-26 |  | Ms: 565 | DMSO-d6: 0.93 (d, 6H), 2.4-2.56 (m, 4H), 2.69 (t, 2H), 3.25-3.38 (m, 1H), 3.59 (t, 4H), 4.11 (t, 1H), 6.75 (dd, 1H), 6.93 (dd, 1H), 7.16-7.23 (m, 1H), 7.3-7.4 (m, 1H), 7.4-7.38 (m, 1H), 7.8 (dd, 1H), 7.88 (d, 1H), 8.19 (s, 1H), 8.36-8.5 (m, 1H), 8.92 (s, 1H), 9.34 (s, 1H) |
| 19-27 |  | Ms: 614 | DMSO-d6: 0.93 (d, 6H), 1.3-1.62 (m, 8H), 1.75-1.85 (m, sH), 2.26-2.4 (m, 1H), 2.4-2.58 (m, 4H), 3.28-3.38 (m, 1H), 3.68-3.78 (m, 5H), 6.42 (dd, 1H), 6.64 (d, 1H), 7.18-7.24 (m, 1H), 7.42-7.5 (m, 2H), 7.77 (d, 1H), 7.82 (dd, 1H), 8.13 (s, 1H), 8.17 (s, 1H), 8.4-8.5 (m, 1H), 9.36 (s, 1H) |

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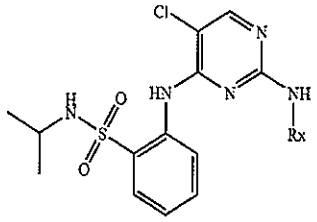
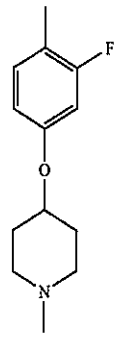
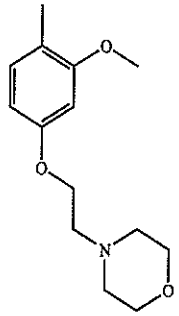
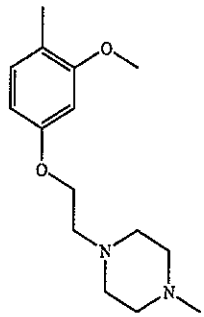
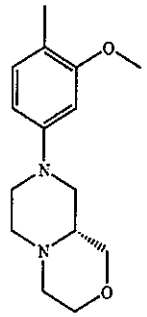


| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-28 |  | Rf: 0.5 (MeOH: CH2Cl2 = 3:7) | DMSO-d6: 0.93 (d, 6H), 1.6-1.7 (m, 2H), 1.88-1.98 (m, 2H), 2.17-2.35 (m, 5H), 2.6-2.73 (m, 2H), 3.25-3.4 (m, 1H), 4.34-4.44 (m, 1H), 6.75 (dd, 1H), 6.93 (dd, 1H), 7.16-7.23 (m, 1H), 7.29-7.36 (m, 1H), 7.37-7.47 (m, 1H), 7.8 (dd, 1H), 7.89 (d, 1H), 8.19 (s, 1H), 8.36-8.46 (m, 1H), 8.92 (s, 1H), 9.31 (s, 1H) |
| 19-29 |  | Ms: 577 | DMSO-d6: 0.93 (d, 6H), 2.45-2.55 (m, 4H), 2.7 (t, 2H), 3.25-3.35 (m, 1H), 3.59 (t, 3H), 3.76 (s, 3H), 4.1 (t, 1H), 6.48 (dd, 1H), 6.65 (d, 1H), 7.18-7.24 (m, 1H), 7.4-7.5 (m, 2H), 7.82 (dd, 1H), 7.88 (d, 1H), 8.17 (s, 1H), 8.24 (s, 1H), 8.4-8.48 (m, 1H), 9.31 (s, 1H) |
| 19-30 |  | Ms: 590 | DMSO-d6: 0.93 (d, 6H), 2.15 (s, 3H), 2.2-2.4 (m, 4H), 2.4-2.6 (m, 4H), 2.69 (t, 2H), 3.25-3.35 (m, 1H), 3.75 (s, 3H), 4.08 (t, 2H), 6.47 (dd, 1H), 6.64 (d, 1H), 7.18-7.24 (m, 1H), 7.41-7.49 (m, 2H), 7.81 (dd, 1H), 7.86-7.91 (m, 1H), 8.17 (s, 1H), 8.24 (s, 1H), 8.39-8.46 (m, 1H), 9.31 (s, 1H) |
| 19-31 |  | Ms: 588 | DMSO-d6: 0.94 (d, 6H), 2.19-2.36 (m, 4H), 2.66-2.85 (m, 3H), 3.15-3.21 (m, 1H), 3.73-3.8 (m, 5H), 6.43 (dd, 1H), 6.63 (d, 1H), 7.18-7.25 (m, 1H), 7.4 (d, 1H), 7.43-7.5 (m, 1H), 7.81 (dd, 1H), 7.89 (d, 1H), 8.16 (s, 1H), 8.17 (s, 1H), 8.42-8.52 (m, 1H), 9.32 (s, 1H) |

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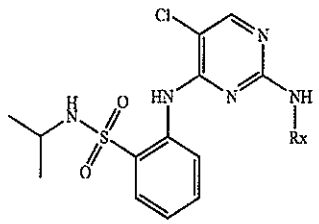
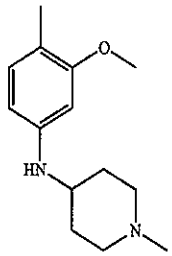
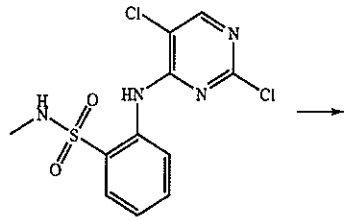
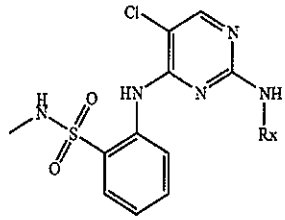
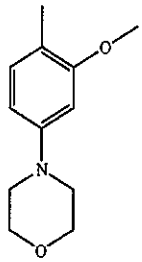


| ExplNo. | Rx | Rf (solvent) Or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 19-32 |  | Ms: 560 | $CDCl_3$: 1.01(s, 6H), 1.45-1.56 (m, 2H), 2.03-2.11 (m, 2H), 2.11-2.2 (m, 2H), 2.31 (s, 3H), 2.78-2.87 (m, 2H), 3.22-3.31 (m, 1H), 3.39-3.5 (m, 1H), 3.82 (s, 3H), 4.5-4.6 (m, 1H), 6.13 (dd, 1H), 6.21 (d, 1H), 7.16 (s, 1H), 7.18-7.24 (m, 1H), 7.5-7.57 (m, 1H), 7.82 (d, 1H), 7.97 (dd, 1H), 8.16 (s, 1H), 8.08 (s, 1H), 8.46(d, 1H), 8.92 (s, 1H) |

The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide and the corresponding aniline following the procedure of Example A





| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-1 |  | 0.50 (AcOEt) | $CDCl_3$: 2.63(d, 3H), 3.14(t, 4H), 3.87-3.90(m, 7H), 4.64(m, 1H), 6.45(dd, 1H), 6.55(d, 1H), 7.23-7.26(m, 1H), 7.51-7.55(m, 1H), 7.91(d, 1H), 7.95(dd, 1H), 8.06(s, 1H), 8.47(d, 1H), 9.26(s, 1H) |

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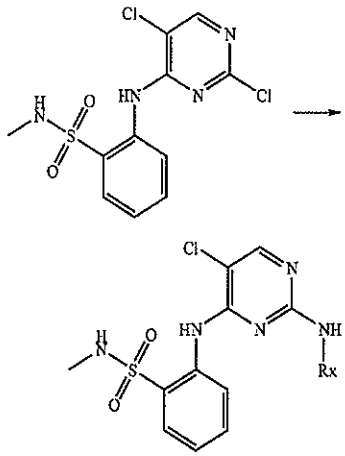
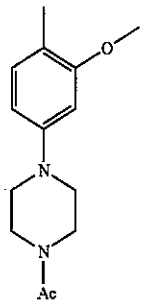
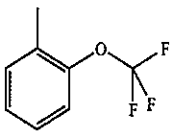
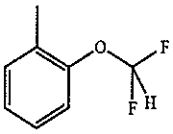
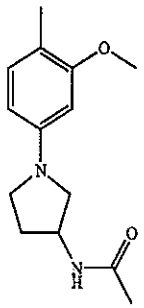


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-2 |  | m/z 546, 548 (M + 1) | DMSO-d6: 2.06 (s, 3H), 2.43 (s, 3H), 3.10 (m, 2H), 3.16 (m, 2H), 3.59-3.62 (m, 4H), 3.77 (s, 3H), 6.49 (dd, 1H), 6.68 (d, 1H), 7.21-7.25 (m, 1H), 7.42 (d, 1H), 7.49 (dd, 1H), 7.75-7.77 (m, 1H), 7.78(s, 1H), 8.16(s, 1H), 8.21 (s, 1H), 8.50(d, 1H), 9.35 (s, 1H) |
| 20-3 |  | 0.27 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.65(d, 3H), 4.45-4.49(m, 1H), 6.99-7.04(m, 1H), 7.17-7.28(m, 4H), 7.56-7.60(m, 1H), 7.96-7.98(m, 1H), 8.18(s, 1H), 8.31-8.34(m, 1H), 8.41-8.44(m, 1H), 9.14(s, 1H) |
| 20-4 |  | 0.27 (n-hexane: AcOEt = 3:1) | $CDCl_3$: 2.65(d, 3H), 4.54-4.58(m, 1H), 6.53(dd, 1H), 6.98-7.02(m, 1H), 7.11-7.15(m, 2H), 7.24-7.28(m, 1H), 7.35(bs, 1H), 7.57-7.61(m, 1H), 7.95-7.98(m, 1H), 8.16(s, 1H), 8.29-8.32(m, 1H), 8.42-8.46(m, 1H), 9.14(s, 1H) |
| 20-5 |  | 0.46 (MeOH: $CH_2Cl_2$ = 1:4) | $CDCl_3$: 1.95-2.00(m, 5H), 2.29-2.37(m, 1H), 2.62(d, 3H), 3.20-3.78(m, 4H), 3.86(s, 3H), 4.60-4.64(m, 2H), 5.68-5.69(m, 1H), 6.09-6.16(m, 2H), 7.15(bs, 1H), 7.19-7.23(m, 1H), 7.54-7.58(m, 1H), 7.88-7.95(m, 2H), 8.06(s, 1H), 8.55-8.57(m, 1H), 9.08(s, 1H) |

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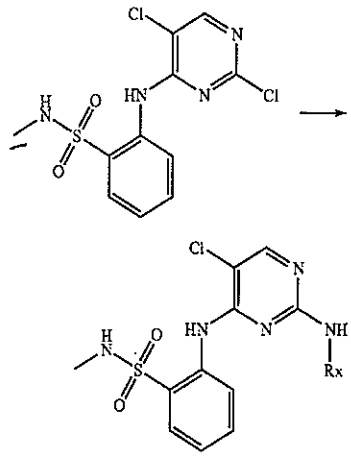
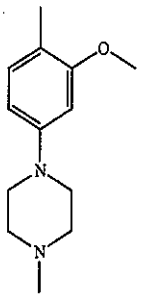
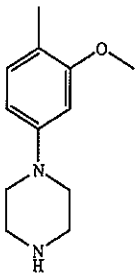
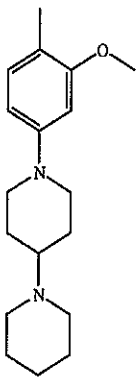


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-6 |  | 518 [M + 1]+ | DMSO-d6: 2.23(s, 3H), 2.43(s, 3H), 2.45-2.50(m, 4H), 3.12-3.17(m, 4H), 3.76(s, 3H), 6.45(dd,1H), 6.63(d, 1H), 7.22(dd, 1H), 7.37(d, 1H), 7.45-7.50(m 1H), 7.74-7.78(m, 1H), 7.76(d, 1H), 8.15(s, 1H), 8.19(s, 1H), 8.46-8.53(m, 1H), 9.35(bs, 1H) |
| 20-7 |  | 504 [M + 1]+ | DMSO-d6: 2.43(s, 3H), 2.80-2.89(m, 4H), 2.99-3.07(m, 4H), 3.76(s, 3H), 6.44(dd,1H), 6.61(d, 1H), 7.18-7.24(m, 1H), 7.37(d, 1H), 7.44-7.50(m, 1H), 7.76(dd, 1H), 8.15(s, 1H), 8.18(s, 1H), 8.45-8.55(m, 1H), 9.20-9.45(m, 1H) |
| 20-8 |  | 586 [M + 1]+ | DMSO-d6: 1.35-1.43(m, 2H), 1.45-1.61 (m, 6H), 1.75-1.85(m,2H), 2.30-2.40(m, 1H), 2.43(d, 3H), 2.42-2.55(m, 4H), 2.60-2.70(m, 2H), 3.68-3.77(m, 2H), 3.75(s, 3H), 6.45(dd, 1H), 6.62(d, 1H), 7.21 (dd, 1H), 7.36(d, 1H), 7.43-7.51(m, 1H), 7.73-7.81(m, 1H), 7.75(dd, 1H), 8.15(s, 1H), 8.17(s, 1H), 8.45-8.52(m, 1H), 9.34(bs, 1H) |

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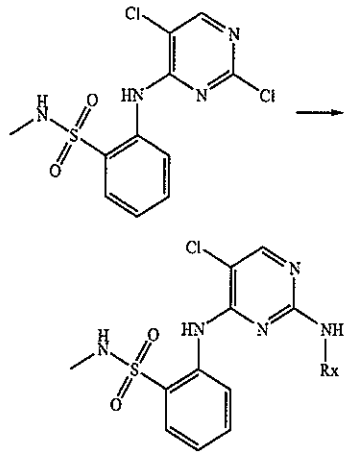
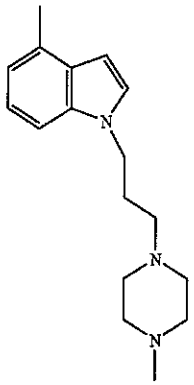
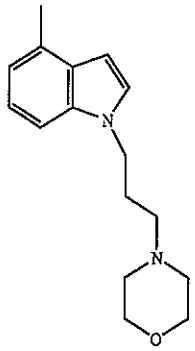
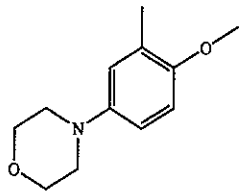


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-9 |  | 569 [M + 1]+ | DMSO-d6: 1.85-1.95(m, 2H), 2.15(s, 3H), 2.18(t, 2H), 2.22-2.40(m, 8H), 2.43(s, 3H), 4.17(t, 2H), 6.65(d, 1H), 7.06(dd, 1H), 7.20(d, 1H), 7.22(ddd, 1H), 7.25(d, 1H), 7.39-7.47(m, 2H), 7.72-7.82(m, 1H), 7.77(dd, 1H), 8.26(s, 1H), 8.52(d, 1H), 9.22(s, 1H), 9.36(s, 1H) |
| 20-10 |  | 556 [M + 1]+ | DMSO-d6: 1.85-1.95(m, 2H), 2.19(t, 2H), 2.25-2.35(m, 4H), 2.43(s, 3H), 3.55-3.60(m, 4H), 4.19(t, 2H), 6.66(d, 1H), 7.06(dd, 1H), 7.17-7.24(m, 1H), 7.21(d, 1H), 7.27(d, 1H), 7.39-7.45(m, 1H), 7.44(d, 1H), 7.70-7.80(m, 1H), 7.76(dd, 1H), 8.26(s, 1H), 8.52(d, 1H), 9.21(s, 1H), 9.36(s, 1H) |
| 20-11 |  | Rf (Hexane: AcOEt = 1:1) 0.29 | DMSO-d6: 2.64 (d, 3H), 2.87-2.96 (m, 4H), 3.65-3.74 (m, 4H), 3.86 (s, 3H), 4.41451 (m, 1H), 6.50 (dd, 1H), 6.81 (d, 1H), 7.55-7.64 (m, 2H), 7.96 (d, 1H), 8.01 (s, 1H), 8.19 (s, 1H), 8.49 (d, 1H), 9.07 (s, 1H). |

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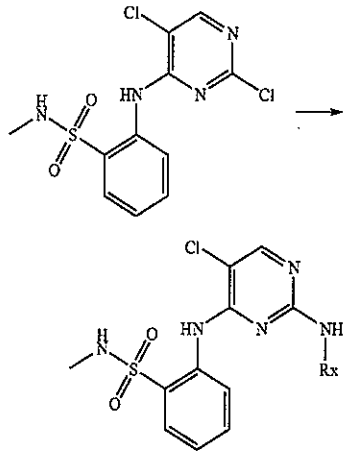
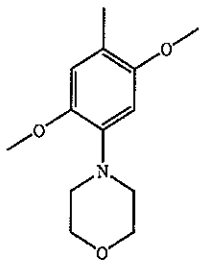
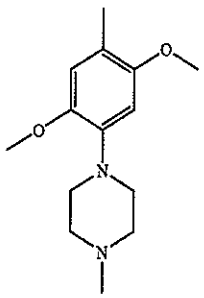
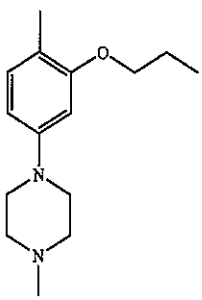


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-12 |  | MS 535 | DMSO-d6: 2.64 (d, 3H), 3.05 (bs, 4H), 3.59 (bs, 3H), 3.87(bs, 3H), 3.89 (bs, 4H), 4.52-4.48 (m, 1H), 6.57(bs, 1H), 7.25-7.20(m, 1H), 7.44-7.32 (m, 1H), 7.63-7.52 (m, 1H), 7.94(bs, 1H), 8.06 (d, 1H), 8.25(s, 1H), 8.48(d, 1H), 9.06(bs, 1H) |
| 20-13 |  | MS 548 | DMSO-d6: 2.17 (bs, 3H), 2.63 (d, 3H), 2.68 (bs, 4H), 3.10(bs, 4H), 3.57 (s, 3H), 4.54-4.46 (m, 1H), 6.59(bs, 1H), 7.27-7.18(m, 1H), 7.37 (bs, 1H), 7.62-7.55 (m, 1H), 7.94(bs, 1H), 7.95 (d. 1H), 8.16(s, 1H), 8.48(d, 1H), 9.04(bs, 1H) |
| 20-14 |  | MS 546 | DMSO-d6: 1.06 (t, 3H), 1.86 (dd, 2H), 2.37 (s, 3H), 2.62-2.59 (m, 4H), 2.64(d, 3H), 4.00-3.97 (m, 4H), 4.62-4.54 (m, 1H), 6.44 (dd, 1H), 6.54(d, 1H), 7.27-7.22(m, 1H), 7.34(bs, 1H), 7.58-7.54(m, 1H), 7.95(dd, 1H), 8.02(d, 1H), 8.11(s, 1H), 8.53(d, 1H), 9.07(bs, 1H) |

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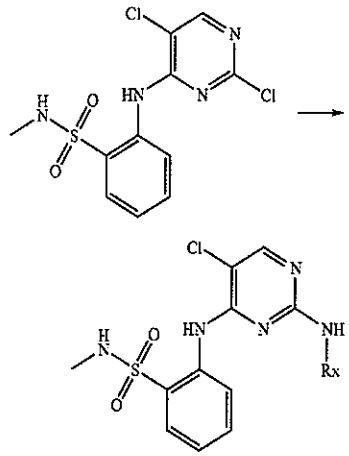
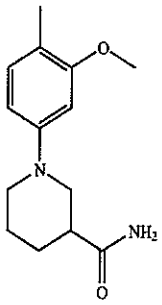
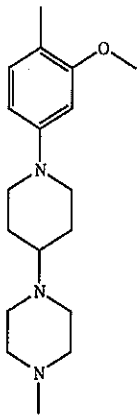
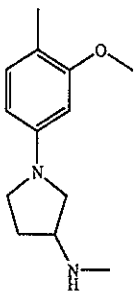


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-15 |  | LC-MS 535 | DMSO-d6: 1.46-1.62 (m, 2H), 1.72-1.79 (m, 1H), 1.82-1.90 (m, 1H), 2.38-2.46 (m, 1H), 2.43 (s, 3H), 2.62-2.76 (m, 2H), 3.59-3.69 (m, 2H), 3.43 (s, 3H), 6.47 (dd, 1H), 6.63 (d, 1H), 6.82-6.89 (br, 1H), 7.21 (dd, 1H), 7.32-7.41 (m, 2H), 7.44-7.52 (m, 1H), 7.71-7.82 (m, 2H), 8.15 (s, 1H), 8.15-8.20 (br, 1H), 8.44-8.53 (m, 1H), 9.28-9.38 (m, 1H) |
| 20-16 |  | 0.24 (CH2Cl2: MeOH = 8:2) | DMSO-d6: 1.47-1.55 (m, 2H), 1.80-1.91 (m, 2H), 2.16 (s, 3H), 2.25-2.41 (m, 5H), 2.42-2.48 (m, 3H), 2.61-2.73 (m, 2H), 3.68-3.79 (m, 5H), 6.45 (dd, 1H), 6.62 (d, 1H), 7.21 (dd, 1H), 7.34 (d, 1H), 7.45-7.49 (m, 1H), 7.73-7.80 (m, 2H), 8.15 (s, 1H), 8.20 (s, 1H), 8.45-8.54 (m, 1H), 9.34 (s, 1H) |
| 20-17 |  | LC-MS 535 | DMSO-d6: 1.76-1.84 (m, 1H), 2.08-2.16 (m, 1H), 2.33 (s, 3H), 2.42 (s, 3H), 3.00-3.03 (m, 1H), 3.23-3.27 (m, 3H), 3.42-3.46 (m, 1H), 3.74 (s, 3H), 6.06 (dd, 1H), 6.18-6.20 (m, 1H), 7.17-7.23 (m, 1H), 7.38-7.48 (br, 1H), 7.72-7.77 (m, 1H), 8.12 (s, 1H), 8.17-8.21 (br, 1H), 8.46-8.58 (br, 1H), 9.30-9.40 (br, 1H) |

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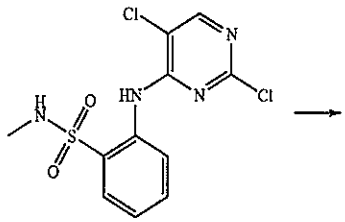
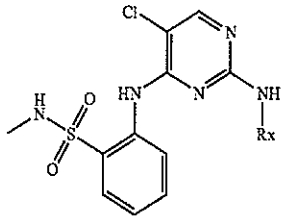
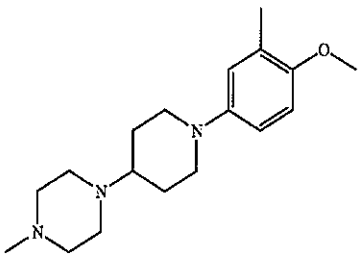
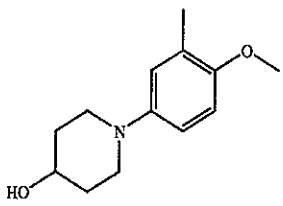
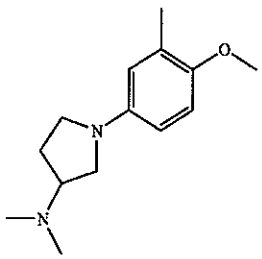




| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-18 |  | LC-MS 601 | DMSO-d6: 1.36-1.49 (m, 2H), 1.69-1.76 (m, 2H), 2.13 (s, 3H), 2.15-2.23 (m, 1H), 2.24-2.36 (br, 4H), 2.39-2.48 (m, 5H), 2.43 (s, 3H), 3.27-3.40 (m, 2H), 3.74 (s, 3H), 6.62 (dd, 1H), 6.90 (d, 1H), 7.22-7.26 (m, 1H), 7.41-7.46 (m, 1H), 7.49-7.53 (m, 1H), 7.55-7.86 (br, 1H), 7.77 (dd, 1H), 8.16 (s, 1H), 8.25 (s, 1H), 8.42 (d, 1H), 9.28 (s, 1H) |
| 20-19 |  | LC-MS 519 | DMSO-d6: 1.37-1.46 (m, 2H), 1.69-1.75 (m, 2H), 2.43 (s, 3H), 2.53-2.61 (m, 2H), 3.18-3.26 (m, 2H), 3.40-3.74 (m, 2H), 4.62 (d, 1H), 6.62 (dd, 1H), 6.90 (d, 1H), 7.22-7.26 (m, 1H), 7.42-7.46 (br, 1H), 7.48-7.55 (m, 1H), 7.77-7.80 (m, 2H), 8.13-8.18 (br, 1H), 8.25 (s, 1H), 8.40-8.45 (m, 1H), 9.25-9.30 (m, 1H) |
| 20-20 |  | LC-MS 532 | DMSO-d6: 1.66-1.76 (m, 1H), 2.00-2.07 (m, 1H), 2.14 (s, 6H), 2.43 (s, 3H), 2.68-2.76 (m, 1H), 2.87-2.91 (m, 1H), 2.99-3.10 (m, 2H), 3.24-3.28 (m, 1H), 3.71 (s, 3H), 6.25 (dd, 1H), 6.90 (d, 1H), 7.00-7.03 (m, 1H), 7.21-7.24 (m, 1H), 7.40-7.45 (m, 1H), 7.78-7.83 (m, 2H), 8.19 (s, 1H), 8.24 (s, 1H), 8.46 (d, 1H), 9.27-9.36 (br, 1H) |

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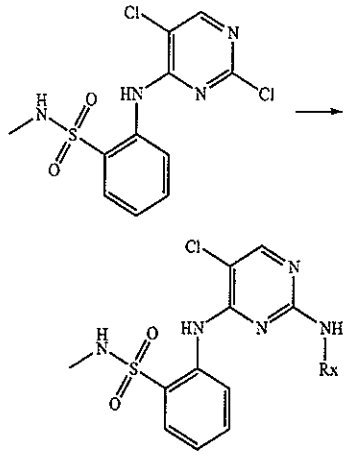
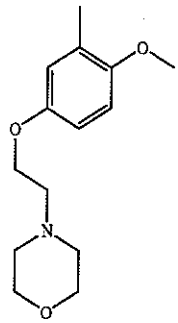
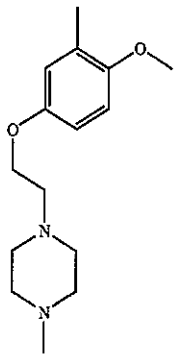
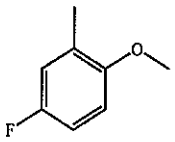
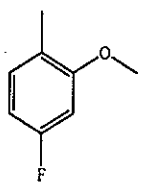


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-21 |  | Me: 549 | DMSO-d6: 2.37-2.47 (m, 4H), 2.48-2.53 (m, 3H), 2.64 (t, 2H), 3.57 (t, 3H), 3.77 (s, 3H), 3.92 (t, 2H), 6.61 (dd, 1H), 6.93 (d, 1H), 7.28 (dd, 1H), 7.56-7.63 (m, 2H), 7.75-7.85 (m, 2H), 7.74-7.84 (m, 2H), 8.14 (s, 1H), 8.29 (s, 1H) 8.46 (d, 1H), 9.33(s, 1H) |
| 20-22 |  | Ms: 562 | DMSO-d6: 2.20 (s, 3H), 2.3-2.5 (m, 11H), 2.64 (t, 2H), 3.77 (s, 3H), 3.91 (t, 2H), 6.61(dd, 1H), 6.94 (d, 1H), 7.25-7.31(m, 1H), 7.57 (d, 1H), 7.58-7.64 (m, 1H), 7.74-7.84 (m, 2H), 8.12 (brs, 1H), 8.28 (s, 1H) 8.46 (d, 1H), 9.33(brs, 1H) |
| 20-23 |  | Ms: 439 | DMSO-d6: 2.42-2.45 (m, 3H), 3.83 (s, 2H), 6.8 (ddd, 1H), 7.02 (dd, 1H), 7.3-7.36 (m, 1H), 7.58-7.64 (m, 1H), 7.74-7.8 (m, 1H), 7.82 (dd, 1H), 7.85 (dd, 1H), 8.18 (brs, 1H), 8.31 (s, 1H), 8.41 (d, 1H), 9.3 (brs, 1H) |
| 20-24 |  | Ms: 438 | DMSO-d6: 2.41-2.45 (m, 3H), 3.79 (s, 2H), 6.74 (ddd, 1H), 7.0 (dd, 1H), 7.22-7.28 (m, 1H), 7.49-7.55 (m, 1H), 7.6 (dd, 1H), 7.75-7.8 (m, 2H), 8.21 (s, 1H), 8.37 (brs, 1H), 8.39-8.45 (m, 1H), 9.34 (brs, 1H) |

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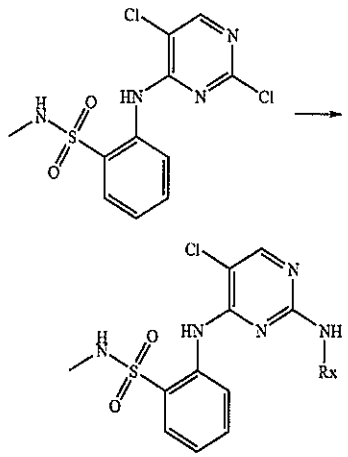
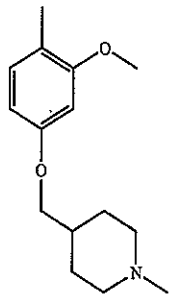
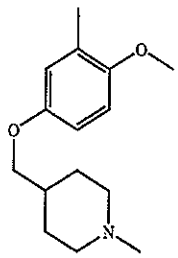
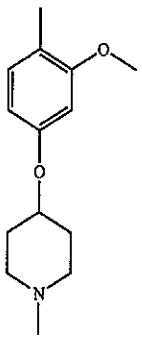


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-25 |  | Ms: 547 | DMSO-d6: 1.24-1.38 (m, 2H), 1.64-1.8 (m, 3H), 1.83-1.92 (m, 2H), 2.16 (s, 3H), 2.41-2.45(m, 3H), 2.76-2.83 (m, 2H), 3.75 (s, 3H), 3.84 (d, 2H), 6.48 (dd, 1H), 6.64 (d, 1H), 7.2-7.25 (m, 1H), 7.41 (d, 1H), 7.43-7.5 (m, 1H), 7.74-7.8 (m, 2H), 8.16 (s, 1H), 8.26 (brs, 1H) 8.44-8.5 (m, 1H), 9.34 (brs, 1H) |
| 20-26 |  | Ms: 547 | DMSO-d6: 1.18-1.3 (m, 2H), 1.56-1.7 (m, 3H), 1.8-1.88 (m, 2H), 2.15 (s, 3H), 2.41-2.45(m, 3H), 2.73-2.8 (m, 2H), 3.75 (s, 3H), 3.65 (d, 2H), 3.77 (s, 3H), 6.57 (dd, 1H), 6.93 (d, 1H), 7.25 (dd, 1H), 7.51-7.6 (m, 2H), 7.7-7.9 (m, 2H), 8.09 (brs, 1H), 8.28 (s, 1H), 8.45 (d, 1H), 9.31 (brs, 1H) |
| 20-27 |  | Ms: 533 | DMSO-d6: 1.62-1.72 (m, 2H), 1.9-1.99 (m, 2H), 2.3-2.35 (m, 5H), 2.41-2.45(m, 3H), 2.64-2.74 (m, 2H), 3.75 (s, 3H), 4.35-4.43 (m, 1H), 6.52 (dd, 1H), 6.65 (d, 1H), 7.19-7.25 (m, 1H), 7.41 (d, 1H), 7.43-7.49 (m, 1H), 7.74-7.8 (m, 2H), 8.16 (s, 1H), 8.27 (brs, 1H), 8.42-8.5 (m, 1H), 9.34 (brs, 1H) |

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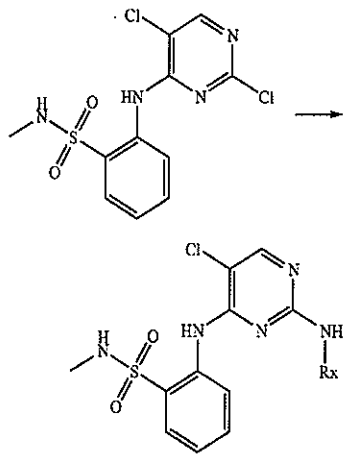
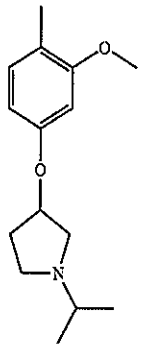
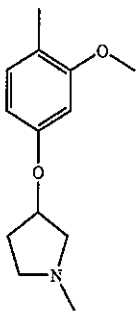
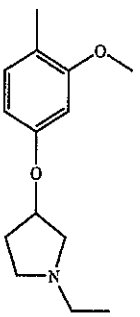


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-28 |  | Ms: 547 | DMSO-d6: 0.96-1.2 (m, 2H), 1.75-1.9 (m, 1H), 2.2-2.3 (m, 1H), 2.35-2.45 (m, 1H), 2.41-2.45(m, 2H), 2.43(d, 3H), 2.6-3.0 (m, 3H), 3.76 (s, 3H), 4.85-5.0 (m, 1H), 6.43-6.49 (m, 1H), 6.57-6.64 (m, 1H), 7.18-7.25 (m, 1H), 7.39-7.52 (m, 2H), 7.73-7.83 (m, 2H), 8.17 (s, 1H), 8.27 (brs, 1H), 8.44-8.51 (m, 1H), 9.35 (brs, 1H) |
| 20-29 |  | Ms: 519 | DMSO-d6: 1.74-1.83 (m, 1H), 2.23-2.31 (m, 1H), 2.28 (s, 3H), 2.35-2.4 (m, 1H), 2.41-2.45(m, 3H), 2.58-2.63 (m, 1H), 2.63-2.7 (m, 1H), 2.78-2.83 (m, 1H), 3.75 (s, 3H), 4.86-4.92 (m, 1H), 6.43 (dd, 1H), 6.58 (d, 1H), 7.19-7.25 (m, 1H), 7.41 (d, 1H), 7.44-7.51 (m, 1H), 7.73-7.83 (m, 2H), 8.16 (s, 1H), 8.26 (brs, 1H), 8.43-8.52 (m, 1H), 9.34 (brs, 1H) |
| 20-30 |  | Ms: 533 | DMSO-d6: 1.04 (t, 3H), 1.74-1.82 (m, 1H), 2.23-2.33 (m, 1H), 2.47-2.5(m, 6H), 2.62-2.72 (m, 2H), 2.8-2.87 (m, 1H), 3.75 (s, 3H), 4.86-4.92 (m, 1H), 6.44 (dd, 1H), 6.59 (d, 1H), 7.19-7.25 (m, 1H), 7.41 (d, 1H), 7.44-7.51 (m, 1H), 7.73-7.8 (m, 2H), 8.16 (s, 1H), 8.26 (brs, 1H), 8.44-8.51 (m, 1H), 9.34 (brs, 1H) |

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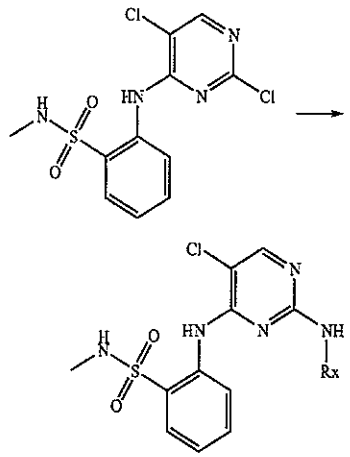
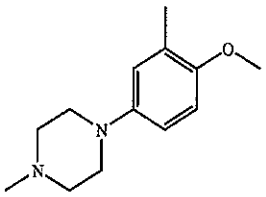
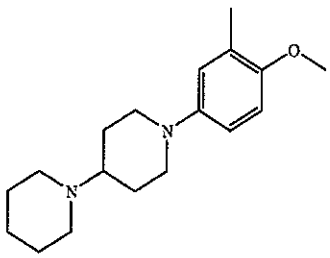
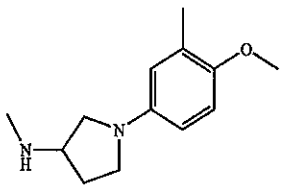
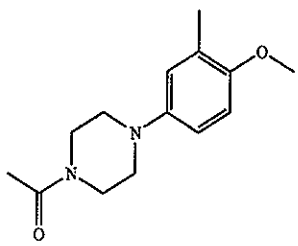


| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-31 |  | Ms: 518 | DMSO-d6: 2.23(s, 3H), 2.38-2.47 (m, 7H), 2.87-2.93 (m, 4H), 3.75 (s, 3H), 6.63 (dd, 1H), 6.93 (d, 1H), 7.22-7.28 (m, 1H), 7.42 (d, 1H), 7.48-7.54 (m, 1H), 7.76-7.84 (m, 1H), 8.2 (s, 1H), 8.25(s, 1H), 8.43 (dd, 1H) 9.29 (s, 1H) |
| 20-32 |  | Ms: 586 | DMSO-d6: 1.35-1.55 (m, 8H), 1.66-1.75 (m, 2H), 2.23(s, 3H), 2.41-2.45 (m, 3H), 3.74 (s, 3H), 6.63 (dd, 1H), 6.91 (d, 1H), 7.21-7.28 (m, 1H), 7.44 (d, 1H), 7.48-7.54 (m, 1H), 7.76-7.87 (m, 1H), 8.16 (s, 1H), 8.25 (s, 1H), 8.43 (dd, 1H) 9.29 (s, 1H) |
| 20-33 |  | Ms: 518 | DMSO-d6: 1.62-1.71 (m, 1H), 1.95-2.04 (m, 1H), 2.23-2.27 (m, 3H), 2.39-2.43 (m, 3H), 2.93-3.1 (m, 2H), 3.13-3.26 (m, 2H), 3.71 (s, 3H), 6.19 (dd, 1H), 6.88 (d, 1H), 7.07-7.13 (m, 1H), 7.13-7.2 (m, 1H), 7.4-7.48 (m, 1H), 7.75 (dd, 1H), 8.06 (brs, 1H), 8.18 (s, 1H), 8.4 (d, 1H) |
| 20-34 |  | Ms: 546 | DMSO-d6: 2.02 (m, 1H), 2.42-2.46 (m, 3H), 2.71-2.91 (m, 4H), 3.44-3.51 (m, 4H), 3.76 (s, 3H), 6.66 (dd, 1H), 6.94 (d, 1H), 7.21-7.27 (m, 1H), 7.75-7.85 (m, 2H), 8.19 (s, 1H), 8.26 (s, 1H), 8.41 (d, 1H), 9.28 (brs, 1H). |

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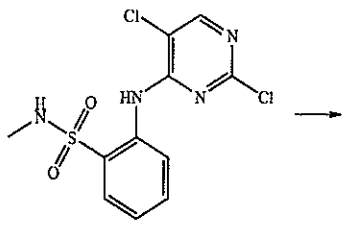
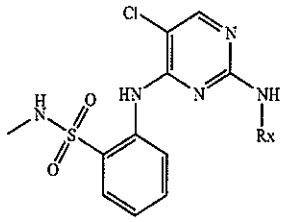
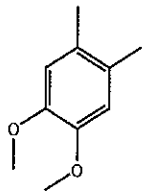
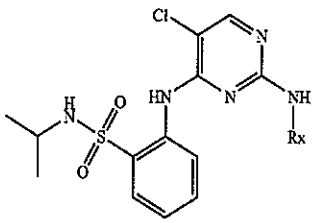
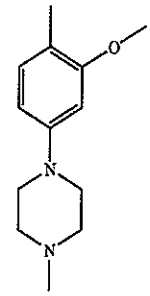




| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 20-35 |  | MS (ESI) 464 (M + H) | HPLC Retention time (min) 2.68 |

The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-sec-butyl-benzenesulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-sec-butyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A



| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 21-1 |  | 0.35 (n-hexane: AcOEt = 1:1) | $CDCl_3$: 0.62(t, 3H), 0.88(d, 3H), 1.22-1.29(m, 2H), 2.23(s,3H), 2.45-2.47(m, 4H), 3.05-3.14(m, 5H), 3.75 (s, 3H), 6.40-6.43(m, 1H), 6.62(s, 1H), 7.18-7.22(m, 1H), 7.39-7.47(m, 2H), 7.80-7.82(m, 1H), 8.15-8.16(m, 2H), 8.44-8.46(m, 1H), 9.32(s |

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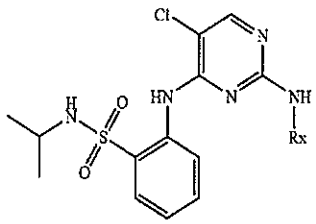
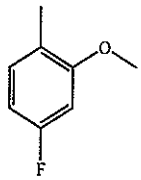
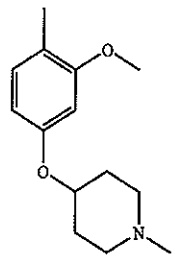
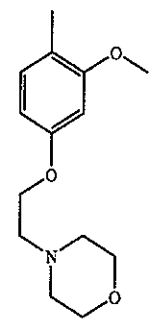
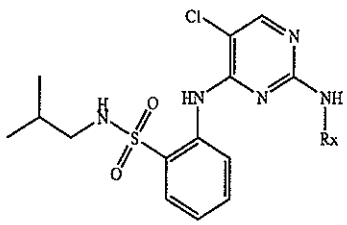
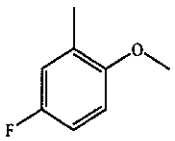
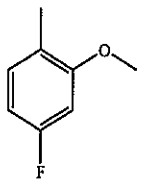
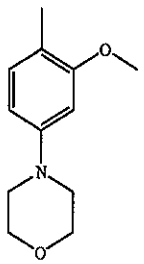


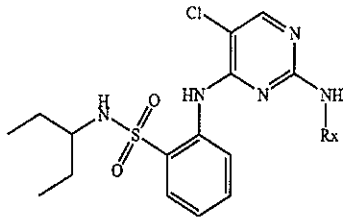
| ExplNo. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 21-2 |  | 0.30 (n-hexane: AcOEt = 3:1) | DMSO-d6: 0.62(t, 3H), 0.87(d, 3H), 1.17-1.26(m, 2H), 3.03-3.10(m, 1H), 3.79(s, 3H), 6.66-6.71(m, 1H), 6.96-7.00(m, 1H), 7.21-7.25(m, 1H), 7.47-7.51(m, 1H), 7.60-7.64(m, 1H), 7.79-7.83(m, 2H), 8.21(s, 1H), 8.31(s, 1H), 8.35-8.37(m, 1H), 9.29(s, 1H) |
| 21-3 |  | 0.30 (n-hexane: AcOEt = 1:1) | DMSO-d6: 0.61(t, 3H), 0.87(d, 3H), 1.21-1.29(m, 2H), 1.58-1.67(m, 2H), 1.86-1.93(m, 2H), 2.14-2.20(m, 5H), 2.59-2.67(m, 2H), 3.06-3.08(m, 1H), 3.74(s, 3H), 4.32-4.36(m, 1H), 6.46-6.48(m, 1H), 6.63(d, 1H), 7.17-7.21 (m, 1H), 7.40-7.50(m, 2H), 7.79-7.81 (m, 2H), 8.16(s, 1H), 8.21(bs, 1H), 8.35-8.42(m, 1H), 9.29(s, 1H) |
| 21-4 |  | 0.30 (n-hexane: AcOEt = 1:1) | DMSO-d6: 0.61 (t, 3H), 0.87(d, 3H), 1.22-1.29(m, 2H), 2.43-2.47(m, 2H), 2.61-2.63(m, 1H), 2.68-2.70(m, 2H), 3.04-3.11(m, 1H), 3.56-3.60(m, 5H), 3.75(s, 3H), 3.93-3.96(m, 1H), 4.08-4.11(m, 2H), 6.45-6.47(m, 1H), 6.64(d, 1H), 7.18-7.22(m, 1H), 7.43-7.46(m, 2H), 7.80-7.82(m, 2H), 8.17(s, 1H), 8.21(s, 1H), 8.42-8.44(m, 1H), 9.31(s, 1H) |

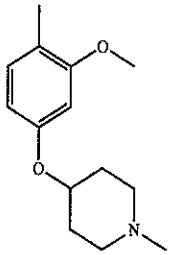
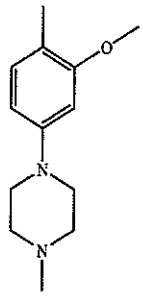
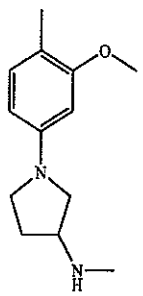
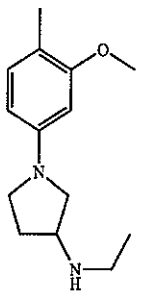
The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-iso-butyl-benzenesulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-sec-butyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A




| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 22-1 |  | 0.30 (n-hexane:AcOEt = 3:1) | DMSO-d6: 0.69(d, 6H), 1.52-1.59(m, 1H), 2.57-2.58 (m, 2H), 3.82(s, 3H), 6.75-6.80(m, 1H), 6.99-7.02 (m, 1H), 7.29-7.33(m, 1H), 7.56-7.60(m, 1H), 7.82-7.93(m, 3H), 8.14(bs, 1H), 8.31(s, 1H), 8.33(s, 1H), 9.23(s, 1H) |
| 22-2 |  | 0.30 (n-hexane:AcOEt = 3:1) | $CDCl_3$: 0.74(d, 6H), 1.57-1.64(m, 1H), 2.72-2.76 (m, 2H), 3.88(s, 3H), 4.55-4.56(m, 1H), 6.52-6.57 (m, 1H), 6.62-6.65(m, 1H), 7.24-7.28(m, 2H), 7.36(bs, 1H), 7.56-7.60(m, 1H), 7.95-8.08(m, 1H), 8.10-8.14 (m, 2H), 8.36-8.39(m, 1H), 8.98(bs, 1H) |
| 22-3 |  | 0.54 (AcOEt) | DMSO-d6: 0.73(d, 6H), 1.55-1.62(m, 1H), 2.56-2.59 (m, 2H), 3.10-3.12(m, 4H), 3.74-3.76(m, 7H), 6.43-6.46(m, 1H), 6.65(d, 1H), 7.20-7.24(m, 1H), 7.40-7.48(m, 2H), 7.76-7.78(m, 1H), 7.90-7.95(m, 1H), 8.16(s, 1H), 8.17(s, 1H), 8.43-8.45(m, 1H), 9.32(s, 1H) |

The following 2-[5-chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-(1-ethyl-propyl)-benzenesulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-(1-ethyl-propyl)-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A



| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 23-1 |  | 0.46 ($MeOH:CH_2Cl_2$ = 3:7) | DMSO-d6: 0.58(t, 6H), 1.14-1.34(m, 4H), 1.58-1.68 (m, 2H), 1.87-1.96(m, 2H), 2.12-2.22(m, 2H), 2.18(s, 3H), 2.57-2.65(m, 2H), 2.86-2.96(m, 1H), 3.75(s, 3H), 4.30-4.39(m, 1H), 6.46(dd, 1H), 6.63(d, 1H), 7.19(dd, 1H), 7.39-7.48(m, 2H), 7.75-7.84(m, 2H), 8.18(s, 1H), 8.20(s, 1H), 8.39(m, 1H), 9.33(bs, 1H) |
| 23-2 |  | 0.35 (n-hexane:AcOEt = 1:1) | $CDCl_3$: 0.59(t, 6H), 1.14-1.34(m, 4H), 2.23(s, 3H), 2.45-2.47(m, 4H), 2.90-2.95(m, 1H), 3.11-3.14(m, 4H), 3.76(s, 3H), 6.39-6.42(m, 1H), 6.62(s, 1H), 7.18-7.22 (m, 1H), 7.41-7.46(m, 2H), 7.76-7.82(m, 2H), 8.12(s, 1H), 8.16(s, 1H), 8.43-8.44(m, 1H), 9.35(s, 1H) |
| 23-3 |  | 0.41 ($MeOH:CH_2Cl_2$ = 1:4) | DMSO-d6: 0.59(t, 6H), 1.16-1.35(m, 4H), 1.75-1.89 (m, 1H), 2.08-2.15(m, 1H), 2.32(s, 3H), 2.90-3.02 (m, 2H), 3.21-3.45(m, 4H), 3.73(s, 3H), 6.02(dd, 1H), 6.18(d, 1H), 7.16(dd, 1H), 7.27(d, 1H), 7.35-7.45 (m, 1H), 7.77-7.82(m, 2H), 8.10(s, 1H) 8.12(s, 1H), 8.45-8.55(m, 1H), 9.38(s, 1H) |
| 23-4 |  | 0.41 ($MeOH:CH_2Cl_2$ = 1:4) | DMSO-d6: 0.60(t, 6H), 1.04(t, 3H), 1.17-1.35(m, 4H), 1.76-1.83(m, 1H), 2.10-2.15(m, 1H), 2.56-2.64(m, 2H), 2.91-3.01(m, 2H), 3.21-3.47(m, 4H), 3.74(s, 3H), 6.02(dd, 1H), 6.18(d, 1H), 7.14-7.17(m, 1H), 7.28(d, 1H), 7.35-7.45(m, 1H), 7.77-7.82(m, 2H), 8.11(s, 1H) 8.12(s, 1H), 8.45-8.55(m, 1H), 9.38(s, 1H) |

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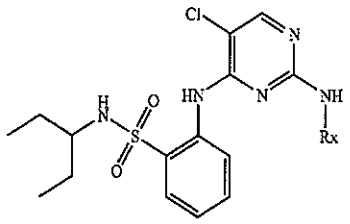
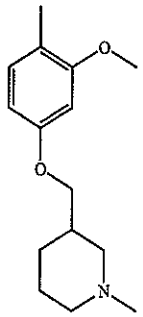
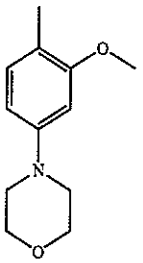
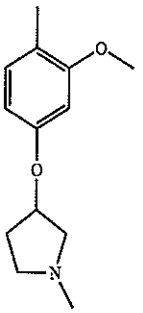
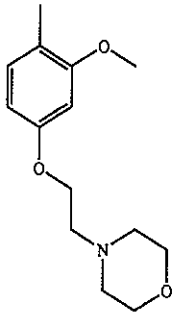


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 23-5 |  | 0.25 (n-hexane:AcOEt = 1:1) | DMSO-d6: 0.58(t, 6H), 1.06-2.16(m, 11H), 2.16(s, 3H), 2.62-2.67(m, 1H), 2.81-2.94(m, 2H), 3.75(s, 3H), 3.80-3.89(m, 2H), 6.41-6.44(m, 1H), 6.62(d, 1H), 7.17-7.21(m, 1H), 7.42-7.47(m, 2H), 7.77-7.82(m, 2H), 8.18(s, 1H), 8.19(s, 1H), 8.35-8.42(m, 1H), 9.35(s, 1H) |
| 23-6 |  | Ms:561 | DMSO-d6: 0.59(t, 6H), 1.14-1.38(m, 4H), 2.87-2.98 (m, 1H), 3.1(t, 4H), 3.72-3.79(m, 7H), 6.42(dd, 1H), 6.64(d, 1H), 7.18-7.24(m, 1H), 7.42-7.5(m, 2H), 7.77(d, 1H), 7.81(dd, 1H), 8.13(s, 1H), 8.17(s, 1H), 8.4-8.5(m, 1H), 9.36(s, 1H) |
| 23-7 |  | Ms:575 | DMSO-d6: 0.58(t, 6H), 1.13-1.37(m, 4H), 1.72-1.82 (m, 1H), 2.21-2.31(m, 4H), 2.32-2.4(m, 1H), 2.54-2.61 (m, 1H), 2.62-2.68(m, 1H), 2.75-2.82(m, 1H), 2.87-2.97(m, 1H), 3.75(s, 3H), 4.84-4.91(m, 1H), 6.37(dd, 1H), 6.56(d, 1H), 7.14-7.24(m, 1H), 7.38-7.52 (m, 2H), 7.72-7.86(m, 1H), 8.12-8.25(m, 2H), 8.34-8.45(M, 1H), 9.33(brs, 1H) |
| 23-8 |  | Ms:605 | DMSO-d6: 0.58(t, 6H), 1.14-1.36(m, 4H), 2.43-2.53 (m, 4H), 2.69(t, 2H), 2.89-2.95(m, 1H), 3.59(t, 4H), 3.76(s, 3H), 4.09(t, 1H), 6.45(dd, 1H), 6.64(d, 1H), 7.17-7.23(m, 1H), 7.41-7.52(m, 2H), 7.78(d, 1H), 7.81(dd, 1H), 8.18(s, 1H), 8.19(s, 1H), 8.36-8.46(m, 1H), 9.35(s, 1H) |

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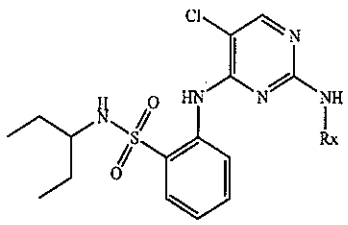
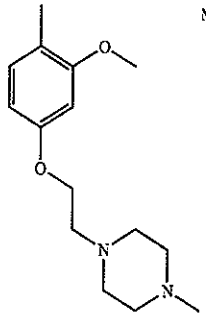
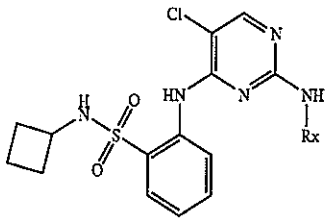
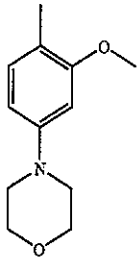


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 23-9 |  | Ms:618 | DMSO-d6: 0.58(t, 6H), 1.14-1.37(m, 4H), 2.15(s, 1H), 2.25-2.4(m, 4H), 2.45-2.55(m, 4H), 2.68(t, 2H), 2.88-2.97(m, 1H), 3.76(s, 3H), 4.07(t, 1H), 6.44(dd, 1H), 6.64(d, 1H), 7.15-7.23(m, 1H), 7.41-7.51(m, 2H), 7.7-7.84(m, 2H), 8.12-8.22(m, 1H), 8.34-8.44 (m, 1H), 9.34(s, 1H) |

The following 2-[chloro-2-(subst.phenylamino)-pyrimidin-4-ylamino]-N-iso-butyl-benzenesulfonamides are prepared from 2-(5-chloro-2-chloro-pyrimidin-4-ylamino)-N-cyclobutyl-benzenesulfonamide and the corresponding aniline following the procedure of Example 7A



| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 24-1 |  | 0.35 (n-hexane:AcOEt = 1:1) | DMSO-d6: 1.37-1.48(m, 2H), 1.69-1.91(m, 4H), 3.09-3.12 (m, 4H), 3.63-3.74(m, 1H), 3.76(s, 3H), 6.43-6.45 (m, 1H), 6.63(d, 1H), 7.18-7.22(m, 1H), 7.41-7.47 (m, 2H), 7.76-7.78(m, 1H), 8.17-8.24(m, 3H), 8.46(d, 1H), 9.33(s, 1H) |

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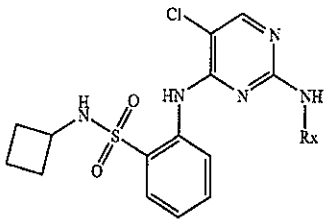
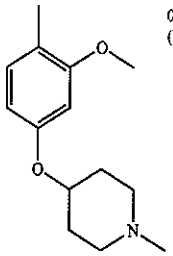
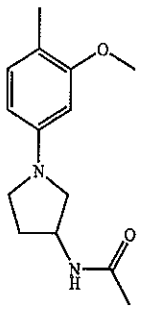
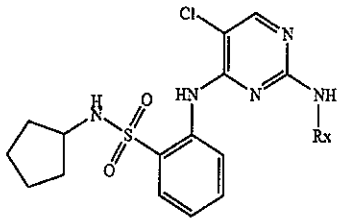
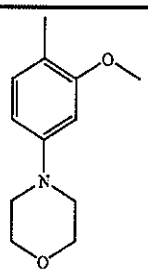


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 24-2 |  | 0.46 ($MeOH:CH_2Cl_2$ = 3:7) | DMSO-d6: 1.37-1.93(m, 10H), 2.18(s, 3H), 2.59-2.62 (m, 1H), 3.60-3.74(m, 1H), 3.77(s, 3H), 4.32-4.36 (m, 1H), 6.46-6.49(m, 1H), 6.62(d, 1H), 7.16-7.20 (m, 1H), 7.41-7.44(m, 2H), 7.75-7.77(m, 1H), 8.16(s, 1H), 8.22(bs, 1H), 8.40-8.42(m, 1H), 9.30(bs, 1H) |
| 24-3 |  | 0.46 ($MeOH:CH_2Cl_2$ = 3:7) | $CDCl_3$: 1.45-1.75(m, 5H), 1.94-2.06(m, 6H), 2.29-2.37 (m, 1H), 3.21-3.56(m, 4H), 3.72-3.81(m, 1H), 3.86(s, 3H), 4.55-4.65(m, 1H), 4.90(d, 1H), 5.72(d, 1H), 6.07(bs, 1H), 6.15(bs, 1H), 7.18-7.22(m, 2H), 7.52-7.56(m, 1H), 7.89-7.94(m, 2H), 8.08(s, 1H), 8.50(d, 1H), 9.00(s, 1H) |



| Expl No. | Rx | Ms | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 25-1 |  | Ms:559 | DMSO-d6: 1.2-1.38(m, 4H), 1.4-1.65(m, 4H), 3.11 (t, 4H), 3.42-3.5(m, 1H), 3.7-3.8(m, 7H), 6.44(dd, 1H), 6.64(d, 1H), 7.18-7.26(m, 1H), 7.38-7.5(m, 2H), 7.81(d, 1H), 7.88-7.96(m, 1H), 8.16(s, 1H), 8.17(s, 1H), 8.4-8.5(m, 1H), 9.34(s, 1H) |

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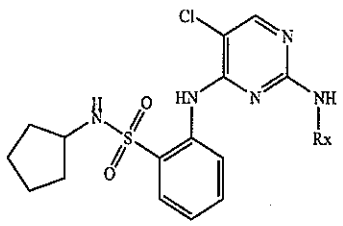
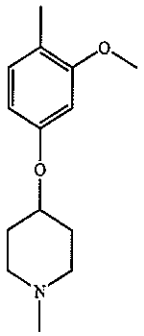
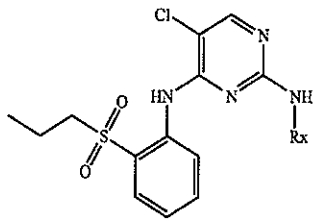
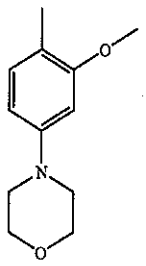


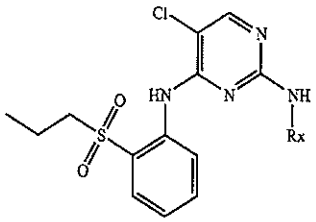
| Expl No. | Rx | Ms | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 25-2 |  | Ms:587 | DMSO-d6: 1.2-1.38(m, 4H), 1.42-1.6(m, 6H), 1.88-1.98 1.98(m, 2H), 2.1-2.25(m, 5H), 2.55-2.65(m, 2H), 3.4-3.5(m, 1H), 3.74(s, 3H), 4.3-4.4(m, 1H), 6.48 (dd, 1H), 6.63(d, 1H), 7.18-7.24(m, 1H), 7.38-7.47 (m, 1H), 7.77-7.82(m, 1H), 7.88-7.96(m, 1H), 8.17(s, 1H), 8.22(s, 1H), 8.36-8.46(m, 1H), 9.31(s, 1H) |

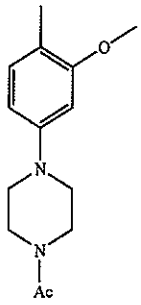
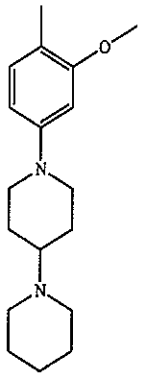
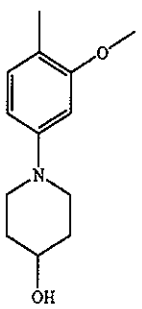
The following 5-Chloro-$N^2$-(substituted phenyl)-$N^4$-[2-(propane-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-1-sulfonyl)-phenyl]-amine and the corresponding aniline following the procedure of Example 7A



| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-1 |  | 0.58 (AcOEt) | $CDCl_3$: 0.97(t, 3H), 1.72-1.82(m, 2H), 3.08-3.14(m, 6H), 3.87-3.89(m, 7H), 6.46(dd, 1H), 6.53(d, 1H), 7.24-7.28 (m, 1H), 7.30(s, 1H), 7.60-7.64(m, 1H), 7.94(dd, 1H), 8.05(d, 1H), 8.15(s, 1H), 8.59(d, 1H), 9.40(s, 1H) |

-continued



| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-2 |  | 0.57 (MeOH:AcOEt = 1:4) | $CDCl_3$: 0.98(t, 3H), 1.85-1.68(m, 2H), 2.15(s, 3H), 3.16-3.07(m, 6H), 3.67-3.62(m, 2H), 3.81-3.78(m, 2H), 3.89(s, 3H), 6.47(d, 1H), 6.55(d, 1H), 7.36-7.33 (m, 1H), 7.62(dd, 1H). 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1) |
| 26-3 |  | 0.13 (MeOH:AcOEt = 1:4) | $CDCl_3$: 0.97(t, 3H), 1.43-1.52(m, 2H), 1.52-1.67(m, 4H), 1.69-1.72(m, 4H), 1.90-1.98(m, 2H), 2.34-2.46 (m, 1H), 2.51-2.59(m, 4H), 2.64-2.74(m, 2H), 3.11(dd, 2H), 3.64-3.73(m, 2H), 3.87(s, 3H), 6.47(dd, 1H), 6.56(d, 1H), 7.24-7.33(m, 1H), 7.62(dd, 1H), 7.94(dd, 1H), 8.00(d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.39(bs, 1H). |
| 26-4 |  | 0.22 (AcOEt) | $CDCl_3$: 0.97(t, 3H), 1.45(d, 1H), 1.68-1.82(m, 4H), 2.0-2.1 (m, 2H), 2.91(ddd, 2H), 3.10(ddd, 2H), 3.46-3.51 (m, 2H), 3.84-3.92(m, 1H), 3.88(s, 1H), 6.48(dd, 1H), 6.57(d, 1H), 7.23-7.32(m, 1H), 7.62(dd, 1H), 7.94(dd, 1H), 8.02(dd, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.39(bs, 1H) |

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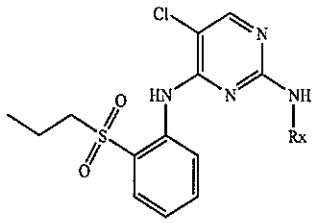
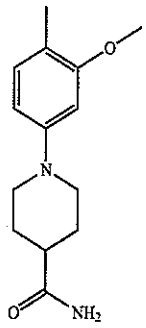
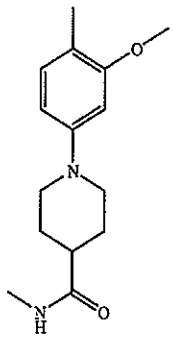
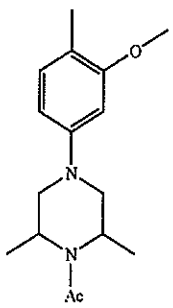


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-5 |  | 0.1 (AcOEt) | $CDCl_3$: 0.97(t, 3H), 1.71-1.82(m, 2H), 1.86-1.98(m, 2H), 2.01-2.08(m, 2H), 2.25-2.37(m, 1H), 2.75(ddd, 2H), 3.10(ddd, 2H), 3.63-3.66(m, 2H), 3.88(s, 3H), 5.25-5.40(m, 1H), 5.40-5.58(m, 1H), 6.48(dd, 1H), 6.57(d, 1H), 7.22-7.34(m, 1H), 7.62(ddd, 1H), 7.93 (d, 1H), 7.94(dd, 1H), 8.02(d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.40(m, 1H) |
| 26-6 |  | MS 587 | $CDCl_3$: 0.97(t, 3H), 1.77(ddd, 2H), 2.00-1.85(m, 4H), 2.27-2.18(m, 1H), 2.72(ddd, 2H) 3.12-3.08(m, 2H), 3.69-3.61(m, 2H), 3.58-3.46(m, 1H), 3.64(t, 2H), 3.80(t, 2H), 3.88(s, 3H), 5.56-5.46(m, 1H), 6.47(dd, 1H), 6.55(d, 1H), 7.32-7.23(m, 1H), 7.30(bs, 1H), 7.64-7.60(m, 1H), 7.94(dd, 1H), 8.02(d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.40(s, 1H) |
| 26-7 |  | MS 587 | $CDCl_3$: 0.98(t, 3H), 1.46(bs, 6H) 1.82-1.73 (m, 2H), 2.17(s, 3H), 3.58-3.46(m, 1H), 2.95-2.84(m, 2H), 3.12-3.08(m, 2H), 3.90(s, 3H), 6.48(dd, 1H), 6.52(d, 1H), 7.30-7.22(m, 1H), 7.31(bs, 1H), 7.66-7.60(m, 1H), 7.95(dd, 1H), 8.06(d, 1H), 8.15(s, 1H), 8.59(d, 1H), 9.43(s, 1H) |

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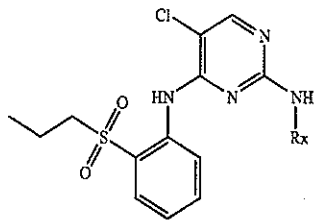
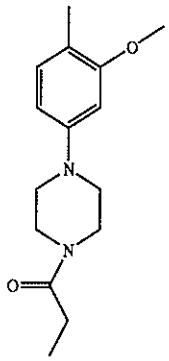
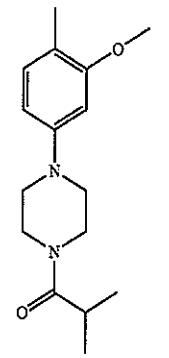
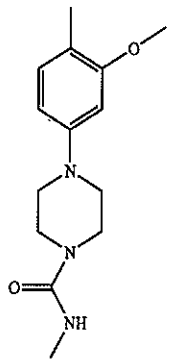


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-8 |  | MS 573 | $CDCl_3$: 0.97(t, 3H), 1.19(t, 3H), 1.77(ddd, 2H), 2.41(m, 2H), 3.18-3.09(m, 6H), 3.68-3.64(m, 2H), 3.85-3.78 (m, 2H), 3.89(s, 3H), 6.47(dd, 1H), 6.55(d, 1H), 7.29-7.25 (m, 1H), 7.34(bs, 1H), 7.64-7.60(m, 1H), 7.95(dd, 1H), 8.07(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H) |
| 26-9 |  | MS 587 | $CDCl_3$: 0.97(t, 3H), 1.17(d, 3H) 1.76(ddd, 2H), 2.88-2.81 (m, 2H), 3.18-3.05(m, 6H), 3.74-3.67(m, 2H), 3.86-3.78(m, 2H), 3.89(s, 3H), 6.47(dd, 1H), 6.55(d, 1H), 7.29-7.20(m, 1H), 7.34(bs, 1H), 7.64-7.60(m, 1H), 7.95(dd, 1H), 8.07(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H) |
| 26-10 |  | MS 517 | $CDCl_3$: 0.97(t, 3H), 1.76(ddd, 2H), 2.86(d, 3H), 3.14-3.08 (m, 2H), 3.13(t, 4H), 3.55 (t, 4H), 3.89(s, 3H), 4.48-4.39(m, 1H), 6.46(dd, 1H), 6.55(d, 1H), 7.29-7.21 (m, 1H), 7.34(bs, 1H), 7.64-7.60(m, 1H), 7.95(dd, 1H), 8.06(d, 1H), 8.15(s, 1H), 9.41(s, 1H) |

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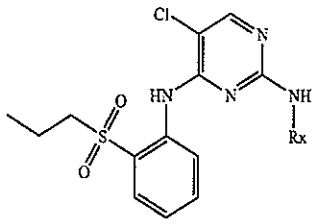
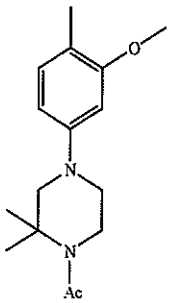
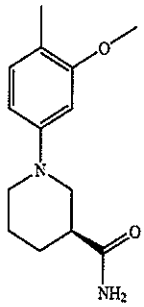
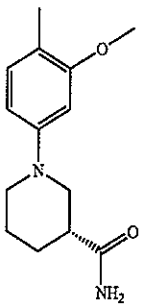
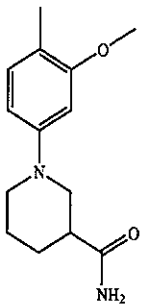


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-11 |  | MS 587 | $CDCl_3$: 0.98(t, 3H), 1.51(s, 6H), 1.82-1.72(m, 1H), 2.13(s, 3H), 3.12-3.08(m, 2H), 3.26(s, 2H), 3.44 (t, 2H), 3.74(t, 2H), 3.88(s, 3H), 5.56-5.46(m, 1H), 6.45(dd, 1H), 6.51(d, 1H), 7.00(bs, 1H), 7.62-7.58(m, 1H), 7.64-7.60(m, 1H), 7.93(d, 1H), 7.96(dd, 1H), 8.13(s, 1H), 8.62(d, 1H), 9.42(s, 1H) |
| 26-12 |  | MS 559 | $CDCl_3$: 0.98(t, 3H), 1.81-1.71(m, 3H), 1.95-1.84(m, 3H), 2.68-2.63(m, 1H), 3.12-3.08(m, 4H), 3.28(d, 2H), 3.89(s, 3H), 5.45-5.38(m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.71-6.62(m, 1H), 7.28-7.21(m, 1H), 7.35(bs, 1H), 7.65-7.61(m, 1H), 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H) |
| 26-13 |  | MS 559 | $CDCl_3$: 0.98(t, 3H), 1.81-1.71(m, 3H), 1.95-1.84(m, 3H), 2.68-2.63(m, 1H), 3.12-3.08(m, 4H), 3.28(d, 2H), 3.89(s, 3H), 5.45-5.38(m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.71-6.62(m, 1H), 7.28-7.21(m, 1H), 7.35(bs, 1H), 7.65-7.61(m, 1H), 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H) |
| 26-14 |  | MS 559 | $CDCl_3$: 0.98(t, 3H), 1.85-1.74(m, 3H), 2.00-1.86(m, 3H), 2.70-2.51(m, 1H), 3.13-3.08(m, 4H), 3.29-3.27 (m, 2H), 3.89(s, 3H), 5.46-5.37(m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.69-6.56(m, 1H), 7.29-7.19(m, 1H), 7.34(bs, 1H), 7.65-7.61(m, 1H), 7.95(dd, 1H), 8.08(d, 1H), 8.15(s, 1H), 8.58(d, 1H), 9.41(s, 1H) |

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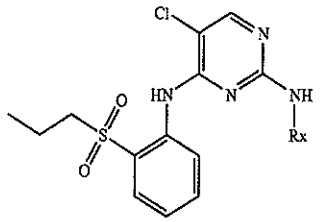
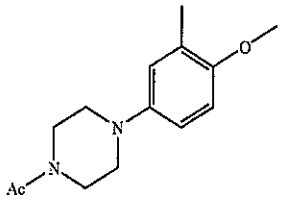
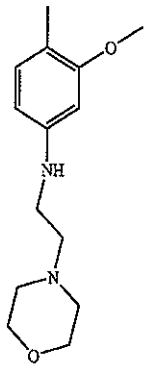
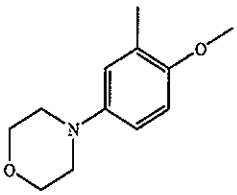
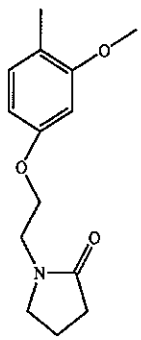


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-15 |  | MS 559 | $CDCl_3$: 0.99(t, 3H), 1.79-1.72(m, 2H), 2.92(t, 2H), 2.98(t, 2H), 3.16-3.12(m, 2H), 3.53(t, 2H), 3.67(t, 2H), 3.87(s, 3H), 6.54(dd, 1H), 6.82(d, 1H), 7.29-7.19(m, 1H), 7.56(bs, 1H), 7.67-7.62(m, 1H), 7.96(dd, 1H), 8.07(d, 1H), 8.21(s, 1H), 8.59(dd, 1H), 9.46(s, 1H) |
| 26-16 |  | MS 561 | $CDCl_3$: 0.98(t, 3H), 1.81-1.72(m, 2H), 2.49(t, 4H), 2.66(t, 2H), 3.12-3.08(m, 2H), 3.18(t, 2H), 3.74(t, 4H), 3.86(s, 3H), 6.53(dd, 1H), 6.20(dd,1H), 6.26(d, 1H), 7.13(bs, 1H), 7.25-7.21(m, 1H), 7.62-7.57(m, 1H), 7.87(dd, 1H), 7.93(dd, 1H), 8.12(s, 1H), 8.62(d, 1H), 9.40(s, 1H) |
| 26-17 |  | MS 518 | $CDCl_3$: 0.98(t, 3H), 1.78-1.73(m, 2H), 2.49(t, 4H), 2.66(t, 2H), 2.94-2.92(m, 4H), 3.15-3.11(m, 2H), 3.76-3.73(m, 4H), 3.88(s, 3H), 6.52(dd, 1H), 6.82(d, 1H), 7.28-7.24(m, 1H), 7.57(bs, 1H), 7.25-7.21(m, 1H), 7.68-7.63(m, 1H), 7.95(dd, 1H), 8.02(d, 1H), 8.20(s, 1H), 8.56(d, 1H), 9.41(s, 1H) |
| 26-18 |  | MS 559 | $CDCl_3$: 0.97(t, 3H), 1.81-1.72(m, 2H), 2.08-2.00(m, 2H), 2.49(t, 4H), 2.66(t, 2H), 2.40(t, 2H), 3.59(t, 2H), 3.69(t, 2H), 3.87(s, 3H), 6.41(dd, 1H), 6.51(d, 1H), 7.29-7.25(m, 2H), 7.65-7.60(m, 1H), 7.95(dd, 1H), 8.05(d, 1H), 8.15(s, 1H), 8.56(d, 1H), 9.41(s, 1H) |

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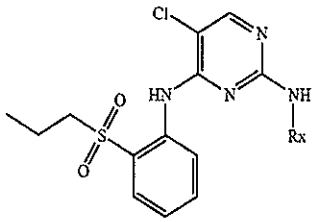
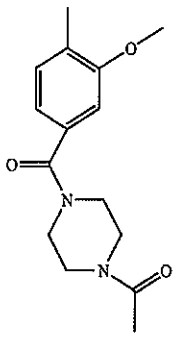
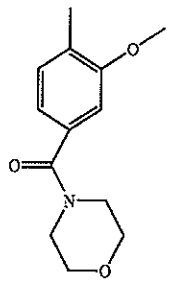
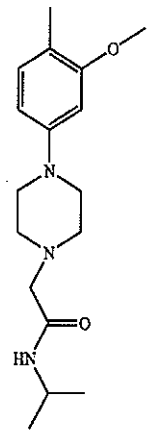


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-19 |  | MS 587 | $CDCl_3$: 0.98(t, 3H), 1.82-1.73(m, 2H), 2.14(s, 3H), 3.12-3.08(m, 2H), 3.55-3.45(m, 2H), 3.66-3.56(m, 4H), 3.79-3.68(m, 2H), 3.95(s, 3H), 6.95(dd, 1H), 7.03 (d, 1H), 7.32-7.28(m, 1H), 7.69-7.64(m, 1H), 7.71(s, 1H), 7.97(dd, 1H), 8.22(s, 1H). 8.39(d, 1H), 8.52(d, 1H), 9.46(s, 1H) |
| 26-20 |  | MS 546 | $CDCl_3$: 0.97(t, 3H), 1.82-1.73(m, 2H), 3.12-3.08(m, 2H), 3.80-3.58(m, 8H), 3.94(s, 3H), 6.94(dd, 1H), 7.02 (d, 1H), 7.32-7.28(m, 1H), 7.69-7.64(m, 1H), 7.32-7.28 (m, 1H), 7.97(dd, 1H), 8.21(s, 1H), 8.34(d, 1H), 8.52(d, 1H), 9.45(s, 1H) |
| 26-21 |  | MS 615 | $CDCl_3$: 0.97(t, 3H), 1.82-1.72(m, 2H), 2.71(t, 3H), 3.05(s, 2H), 3.10(m, 2H), 3.18(t, 4H), 3.88(s, 3H), 4.17-4.08(m, 1H), 6.47(dd, 1H), 6.54(d, 1H), 6.99-6.89 (m, 1H), 7.28-7.24(m, 1H), 7.31(bs, 1H), 7.65-7.60 (m, 1H), 7.32-7.28(m, 1H), 7.95(dd, 1H), 8.05 (d, 1H), 8.15(s, 1H), 8.59(d, 1H), 9.41(s, 1H) |

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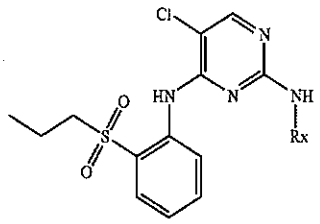
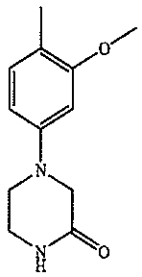
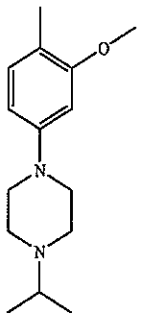
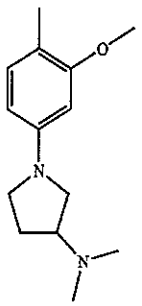
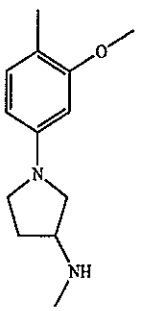


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-22 |  | MS 530 | $CDCl_3$: 0.98(t, 3H), 1.80-1.74(m, 2H), 3.12-3.08(m, 2H), 3.45-3.42(m, 2H), 3.55-3.53(m, 2H), 3.87 (s, 2H), 3.89(s, 3H), 5.98-5.89(m, 1H), 6.44(dd, 1H), 6.50(d, 1H), 7.35-7.19(m, 2H), 7.62-7.58(m, 1H), 7.95(dd, 1H), 8.09(d, 1H), 8.15(s, 1H), 8.57(d, 1H), 9.43(s, 1H) |
| 26-23 |  | MS 558 | $CDCl_3$: 0.97(t, 3H), 1.10(s, 3H), 1.12(s, 3H), 1.80-1.74 (m, 2H), 2.80-2.63(m, 5H), 3.12-3.08(m, 2H), 3.19-3.17(m, 4H), 3.87(s, 3H), 6.48(dd, 1H), 6.56(d, 1H), 7.30-7.23(m, 2H), 7.62-7.58(m, 1H), 7.94(dd, 1H), 8.00(d, 1H), 8.14(s, 1H), 8.59(d, 1H), 9.40(s, 1H) |
| 26-24 |  | MS 544 | $CDCl_3$: 0.98(t, 3H), 1.81-1.72(m, 2H), 2.03-1.91(m, 1H), 2.28-2.19(m, 1H), 2.33(s, 6H), 2.92-2.84(m, 1H), 3.12-3.08(m, 2H), 3.17(t, 1H), 3.35(ddd, 1H), 3.51-3.42(m, 2H), 3.87(s, 3H), 6.11(dd, 1H), 6.14 (d, 1H), 7.09(s, 1H), 7.26-7.20(m, 1H), 7.60-7.56(m, 1H), 7.85(d, 1H), 7.92(dd, 1H), 8.11(s, 1H), 8.38(d, 1H), 9.41(s, 1H) |
| 26-25 |  | MS 530 | $CDCl_3$: 0.98(t, 3H), 1.82-1.71(m, 2H), 1.96-1.86(m, 1H), 2.33-2.20(m, 1H), 2.51(s, 1H), 3.17-3.08(m, 3H), 3.35-3.30(m, 1H), 3.54-3.30(m, 3H), 3.87(s, 3H), 6.12(dd, 1H), 6.16(d, 1H), 7.09(s, 1H), 7.32-7.21 (m, 1H), 7.58 (dd, 1H), 7.85(d, 1H), 7.92(dd, 1H), 8.11(s, 1H), 8.64(d, 1H), 9.40(s, 1H) |

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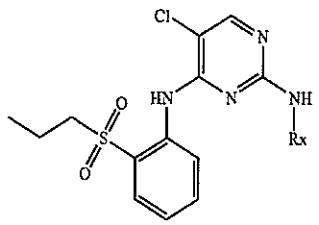
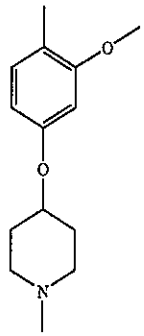
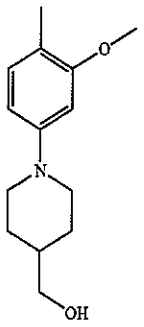
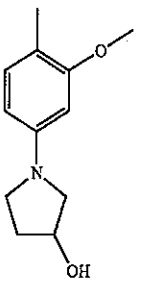


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-26 |  | MS 546 | $CDCl_3$: 0.98(t, 3H), 1.83-1.71(m, 2H), 1.98-1.81(m, 2H), 2.16-2.02(m, 2H), 2.53-2.28(m, 5H), 2.87-2.72 (m, 2H), 3.12-3.08(m, 2H), 3.88(s, 3H), 4.32(bs, 3H), 6.44(dd, 1H), 6.53(d, 1H), 7.32-7.25(m, 2H), 7.63-7.59(m, 2H), 7.94(dd, 1H), 8.04(d, 1H), 8.15(s, 1H), 8.57(d, 1H), 9.42(s, 1H) |
| 26-27 |  | MS 545 | $CDCl_3$: 0.97(t, 3H), 1.38-1.30(m, 1H), 1.49-1.40(m, 2H), 1.70-1.62(m, 1H), 1.83-1.72(m, 2H), 1.89(d, 2H), 2.74-2.10(m, 2H), 3.12-3.08(m, 2H), 3.57(d, 2H), 3.63(d, 2H), 3.90(s, 3H), 6.50(d, 1H), 6.58(s, 1H), 7.34-7.24(m, 2H), 7.64-7.60(m, 1H), 7.94(dd, 1H), 8.02(d, 1H), 8.14(s, 1H), 8.60(dd, 1H), 9.40(s, 1H) |
| 26-28 |  | MS 517 | $CDCl_3$: 0.97(t, 3H), 1.88-1.65(m, 3H), 2.05-1.97(m, 2H), 2.21-2.08(m, 1H), 2.67-2.55(m, 4H), 2.78-2.71 (m, 2H), 3.12-3.08(m, 2H), 3.61(d, 2H), 3.87 (s, 3H), 6.47(dd, 1H), 6.56(d, 1H), 7.28-7.23(m, 2H), 7.64-7.60(m, 1H), 7.94(dd, 1H), 7.99(d, 1H), 8.13(s, 1H), 8.60(dd, 1H), 9.39(s, 1H) |

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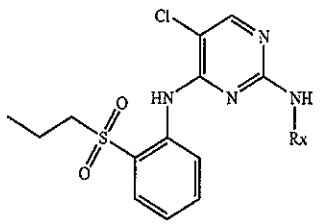
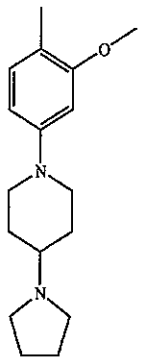
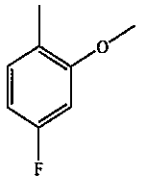
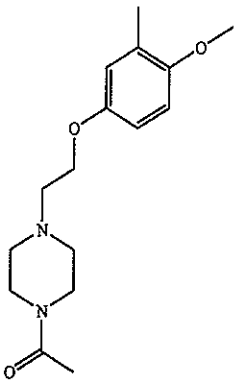
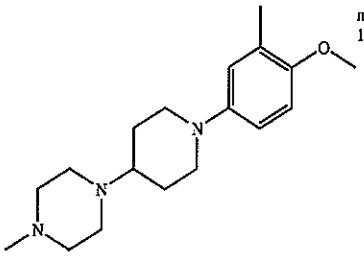


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-29 |  | MS 585 | $CDCl_3$: 0.97(t, 3H), 1.89-1.65(m, 8H), 2.03(d, 2H), 2.20-2.10(m, 1H), 2.68-2.58(m, 4H), 2.78-2.72(m, 2H), 3.12-3.08(m, 2H), 3.61(d, 2H), 3.87(s, 3H), 6.47 (dd, 1H), 6.56(d, 1H), 7.30-7.23(m, 2H), 7.64-7.60(m, 1H), 7.94(dd, 1H), 7.99(dd, 1H), 8.13(s, 1H), 8.60(dd, 1H), 9.39(s, 1H) |
| 26-30 |  | MS 451, 453 | 0.97(t, 3H), 1.71-1.82(m, 2H), 3.06-3.14(m, 2H), 3.89(s, 1H), 6.60(ddd, 1H), 6.66(dd, 1H), 7.25-7.30 (m, 1H), 7.35(br.s, 1H), 7.63(dd, 1H), 7.95(dd, 1H), 8.09-8.18(m, 1H), 8.17(s, 1H), 8.52(dd, 1H), 9.42(s, 1H). |
| 26-31 |  | MS 647, 649 | 0.98(t, 3H), 1.71-1.83(m, 2H), 2.18(s, 3H), 2.47-2.64 (m, 4H), 2.72-2.84(m, 2H), 3.08-3.15(m, 2H), 3.42-3.54 (m, 2H), 3.58-3.69(m, 2H), 3.84(s, 3H), 3.94-4.03 (m, 2H), 6.45-6.51(m, 1H), 6.78(d, 1H), 7.22-7.27 (m, 1H), 7.60(s, 1H), 7.67-7.74(m, 1H), 7.93-7.97 (m, 1H), 7.73(d, 1H), 8.02(s, 1H), 8.54(d, 1H), 9.33(s, 1H). |
| 26-32 |  | m.p. 139.4 | 400 MHz, CDCl3, δ(ppm): 0.98(t; 3H), 1.55-1.90(m; 6H), 2.38(s; 3H), 2.45-2.80(m; 6H), 3.13(m; 2H), 3.47(m; 2H), 3.84(s; 3H), 6.54(dd; 1H), 6.79(d; 1H), 7.23(dd; 1H); 7.51(s; 1H), 7.64(dd: 1H), 7.92(d; 1H), 8.00(s; 1H), 8.19(s; 1H), 8.57(d; 1H), 9.41(s; 1H). |

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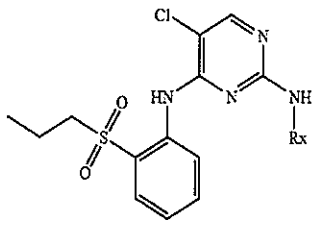
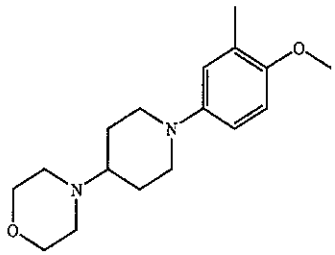
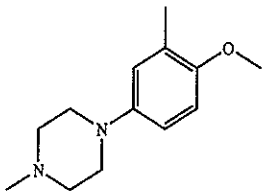
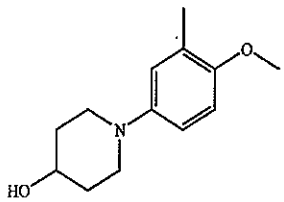
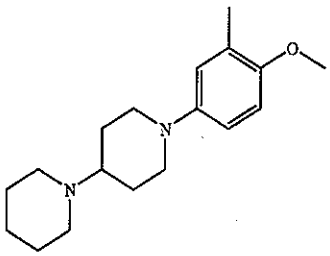
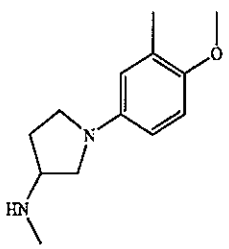


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-33 |  | m.p. 163.4 | 400 MHz, CDCl3, δ(ppm): 0.98(t; 3H), 1.50-1.90(m; 6H), 2.24(bs; 1H), 2.45-2.65(m; 6H), 3.12(m; 2H), 3.45(m; 2H), 3.77(m; 4H9, 3.85(s; 3H), 6.55(dd; 1H); 6.79(d; 1H), 7.24(dd; 1H). 7.52(s; 1H), 7.64 (dd; 1H), 7.93(d; 1H), 8.01(s; 1H), 8.20(s; 1H9, 9.42 (s; 1H). |
| 26-34 |  | m.p. 232.9 | 400 MHz, CDCl3, δ(ppm): 1.00(s; 3H), 1.78(m; 2H), 2.83(s; 3H), 3.03(m; 2H), 3.12(m; 2H), 3.38-3.60(m; 8H), 3.88(s; 3H), 6.56(m; 1H), 6.82(d; 1H), 7.29(m; 1H), 7.60(s; 1H), 7.64(m; 1H), 7.95(d; 1H), 8.12(s; 1H), 8.20(s; 1H), 8.59(d; 1H), 9.50(s; 1H). |
| 26-35 |  | m.p. 197.3 | 400 MHz, CDCl3, δ(ppm): 0.99(t; 3H), 1.43(m; 1H), 1.63(m; 2H), 1.77(m; 2H), 1.90(m; 2H), 2.70(m; 2H), 3.13(m; 2H), 3.28(m; 2H), 3.75(s; 1H), 3.84(s; 3H), 6.55(m; 1H), 6.80(d; 1H), 7.24(m; 1H), 7.53(s; 1H), 7.64(s; 1H), 7.93(d; 1H), 8.02(s; 1H), 8.20(s; 1H), 8.58(d; 1H), 9.41(s; 1H). |
| 26-36 |  | m.p. 147.6 | 400 MHz, CDCl3, δ(ppm): 1.00(t; 3H), 1.78(m; 2H), 3.12(m; 2H), 3.56(m; 1H), 3.87(s; 3H), 6.53(dd; 1H), 6.80(d; 1H), 7.30(dd; 1H), 7.52(s; 1H), 7.64(m; 1H), 7.95(dd; 1H), 8.08(s; 1H), 8.20(s; 1H), 8.60(d; 1H), 9.48(s; 1H). |
| 26-37 |  | m.p. 143.2 | 500 MHz, CDCl3, δ(ppm): 0.96(t; 3H), 1.70(m; 2H), 2.11(m; 1H), 2.39(m; 1H), 2.75(s; 3H), 3.02(m; 1H), 3.22(m; 2H), 3.43(d; 2H), 3.82(s; 3H), 3.86(m; 1H), 6.40(dd; 1H), 6.94(d; 1H), 7.34(ddd; 1H), 7.47(s; 1H), 7.63(ddd; 1H), 7.93(dd; 1H), 8.18(s; 1H), 8.51 (d; 1H). |

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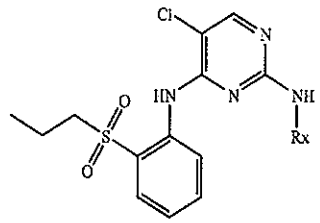
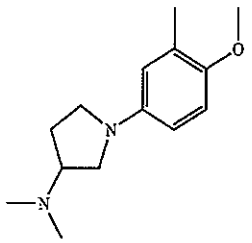
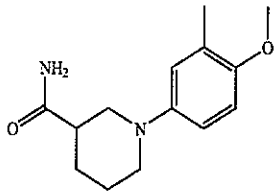
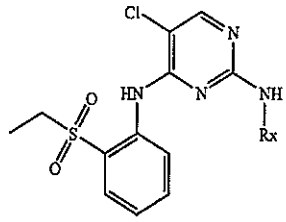
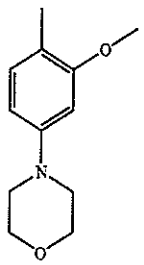


| Expl No. | Rx | Rf (solvent), MS or Mp | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 26-38 |  | m.p. 133.5 | 400 MHz, CDCl3, δ(ppm): 1.00(t; 3H), 1.70-1.95(m; 6H), 2.63(s; 1H), 2,92(s; 1H), 3.00-3.25(m; 5H), 3.89(s; 3H), 5.42(s; 1H), 6.70(s; 1H), 6.83(m; 2H), 7.25(m; 1H), 7.55(s; 1H), 7.63(m; 1H9, 8.95(m; 1H), 8.15(s; 1H), 8.23(s; 1H), 8.54(d; 1H), 9.45(s; 1H). |
| 26-39 |  | m.p. 188.8 | 400 MHz, CDCl3, δ(ppm): 0.99(t; 3H), 1.70-1.90(m; 3H), 2.08(m; 1H), 2.28(s; 6H9, 2.83(s; 1H), 3.00-3.23 (m; 4H9, 3.37(m; 1H), 3.83(s; 3H), 6.19(dd; 1H), 6.83(d; 1H), 7.23(dd; 1H), 7.50(s; 1H), 7.59(m; 2H), 7.93(d; 1H), 8.19(s; 1H), 8.60(d; 1H), 9.42(s; 1H). |

The following 5-Chloro-$N^2$-(substituted phenyl)-$N^4$-[2-ethanesulfonyl-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-ethanesulfonyl-phenyl]-amine and the corresponding aniline following the procedure of Example 7A



| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 27-1 |  | 0.53 (AcOEt) | $CDCl_3$: 1.28(t, 3H), 3.12-3.19(m, 6H), 3.87-3.89(m, 7H), 6.45(dd, 1H), 6.53(d, 1H), 7.24-7.28(m, 1H), 7.31(s, 1H), 7.60-7.64(m; 1H), 7.95(dd, 1H), 8.04(d, 1H), 8.14(s, 1H), 8.58(d, 1H), 9.39(s, 1H) |

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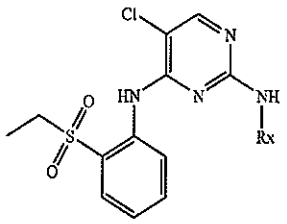
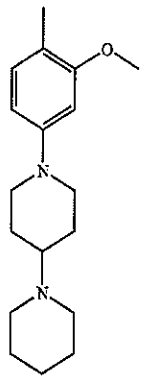
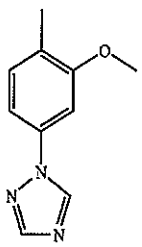
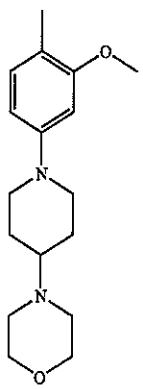


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 27-2 |  | 585 (M + H) | 2.38 |
| 27-3 |  | 486 (M + H) | 3.07 |
| 27-4 |  | 587 (M + H) | 2.29 |

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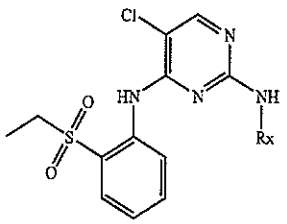
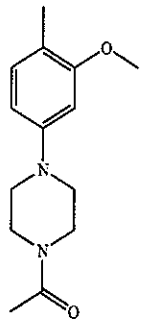
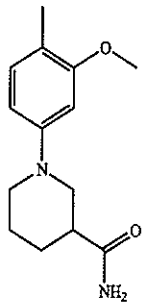
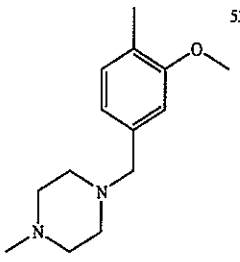


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 27-5 |  | 545 (M + H) | 2.59 |
| 27-6 |  | 545 (M + H) | 2.45 |
| 27-7 |  | 531 (M + H) | 2.25 |

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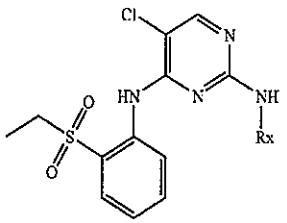
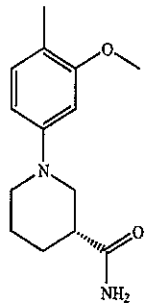
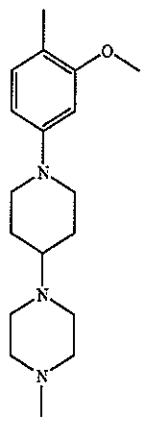
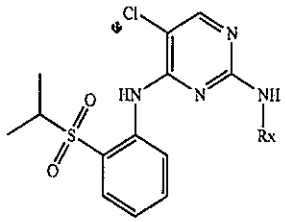
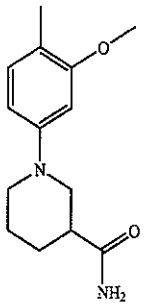
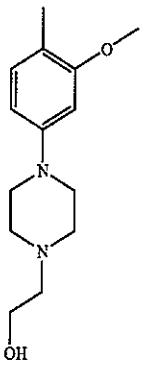
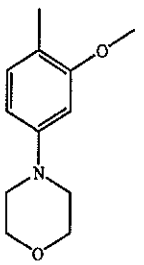


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 27-8 |  | 545 (M + H) | 2.45 |
| 27-9 |  | 600 (M + H) | 2.17 |

HPLC condition
Column: YMC CombiScreen ODS-A (5 um, 12 nm), 50 x 4.6 mm I.D.
Flow rate: 2.0 ml/min
Eluent: A) TFA/water (0.1/100), B) TFA/acetonitrile (0.1/100)
Gradient 5-100% B (0-5 min)
Detection: UV at 215 nm

The following 5-Chloro-$N^2$-(substituted phenyl)-$N^4$-[2-(propane-2-sulfonyl)-phenyl]-pyrimidine-2,4-diamine are prepared from (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-2-sulfonyl)-phenyl]-amine and the corresponding aniline following the procedure of Example 7A




| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-1 |  | 0.2 (AcOEt) | $CDCl_3$: 1.31(d, 6H), 1.85-1.73(m, 1H), 1.86-1.98(m, 3H), 2.62-2.70(m, 1H), 3.11-3.13(m, 2H), 3.21-8.28 (m, 1H), 3.28(m, 2H), 3.88 8s, 3H), 5.41(brs, 1H), 6.53(d, 1H), 6.59(d, 1H), 6.64(brs, 1H), 7.28-7.34 (m, 1H), 7.34(s, 1H), 7.60-7.67(m, 1H), 7.91(dd, 1H), 8.08(d, 1H), 8.13(s, 1H), 8.60(d, 1H), 9.55(s, 1H). |
| 28-2 |  | MS m/z 561, 563 (M + 1). | $CDCl_3$: 1.31(d, 6H), 2.64(t, 2H), 2.68-2.77(m, 4H), 3.19(t, 4H), 3.17-3.28(m, 1H), 3.68(t, 2H), 3.88(s, 3H), 6.48(dd, 1H), 6.55(d, 1H), 7.23-7.32(m, 1H), 7.62(ddd, 1H), 7.91(dd, 1H), 8.04(dd, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.54(bs, 1H) |
| 28-3 |  | 0.55 (AcOEt) | $CDCl_3$: 1.31(d, 6H), 3.12-3.14(m, 4H), 3.21-3.27(m, 1H), 3.87-3.89(m, 7H), 6.46(dd, 1H), 6.53(d, 1H), 7.23-7.27 (m, 1H), 7.30(s, 1H), 7.59-7.64(m, 1H), 7.91(dd, 1H), 8.05(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.55(s, 1H) |

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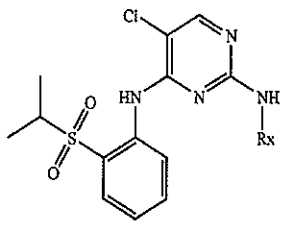
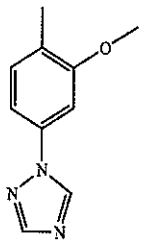
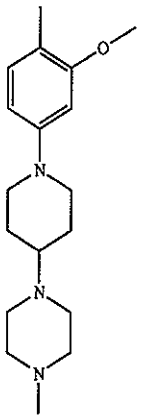
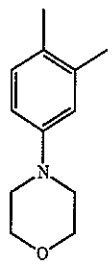
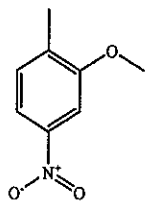


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-4 |  | 0.37 (AcOEt) | $CDCl_3$: 1.32(d, 6H), 3.21-3.27(m, 1H), 4.00(s, 1H), 7.11(dd, 1H), 7.26-7.27(m, 1H), 7.29-7.33(m, 1H), 7.64(s, 1H), 7.66-7.71(m, 1H), 7.95(dd, 1H), 8.10(s, 1H), 8.21(s, 1H), 8.46(d, 1H), 8.50(s, 1H), 8.54(d, 1H), 9.59(s, 1H) |
| 28-5 |  | 0.03 (AcOEt) | $CDCl_3$: 1.31(d, 6H), 1.67-1.77(m, 2H), 1.95-2.05(m, 2H), 2.39-2.48(m, 1H), 2.48-2.61(m, 2H), 2.63-2.78 (m, 8H), 3.24(sept, 1H), 3.71-3.63(m, 2H), 3.87(s, 3H), 6.47(dd, 1H), 6.55(d, 1H), 7.21-7.28(m, 1H), 7.61(ddd, 1H), 7.91(dd, 1H), 8.00(dd, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.53(bs, 1H) |
| 28-6 |  | 502 (M + H) | 2.84 |
| 28-7 |  | 478 (M + H) | 4.53 |

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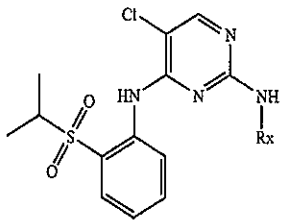
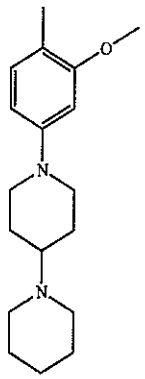
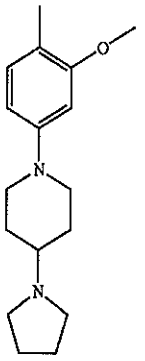
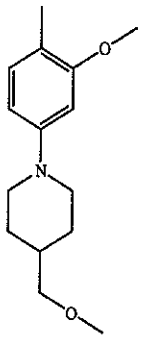


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-8 |  | MS 599 | $CDCl_3$: 1.31(d, 6H), 1.51-1.42(m, 2H), 1.67-1.53(m, 4H), 1.81-1.68(m, 2H), 1.96-1.89(m, 2H), 2.47-2.36 (m, 1H), 2.57-2.54(m, 4H), 2.69(dd, 2H) 3.24(sept, 1H), 3.67(d, 1H), 3.87(s, 1H), 6.48(dd, 1H), 6.56(d, 1H), 7.31-7.21(m, 1H), 7.63-7.59(m, 1H), 8.00(d, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.55(s, 1H) |
| 28-9 |  | MS 585 | $CDCl_3$: 1.26(t, 3H), 1.31(d, 6H), 1.74-1.68(m, 2H), 1.85-1.76(m, 4H), 2.08-1.98(m, 2H), 2.19-2.10(m, 2H), 2.67-2.58(m, 4H), 2.79-2.72(m, 2H), 3.24(sept, 1H) 3.61(d, 2H), 3.87(s, 3H), 6.48(dd, 1H), 6.56(d, 1H), 7.29-7.22(m, 1H), 7.62(dd, 1H), 7.90(dd, 1H), 7.99(d, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.53(s, 1H) |
| 28-10 |  | MS 559 | $CDCl_3$: 1.31(d, 6H), 1.59-1.37(m, 2H), 1.81-1.69(m, 1H), 1.87(d, 2H), 2.73-2.67(m, 2H), 3.28-3.21(m, 1H), 3.37(s, 3H), 3.61(d, 1H), 3.87(s, 3H), 6.49(dd, 1H), 6.57(s, 1H), 7.31-7.21(m, 1H), 7.64-7.60(m, 1H), 7.91(dd, 1H), 8.00(d, 1H), 8.60(d, 1H) 9.53(s, 1H) |

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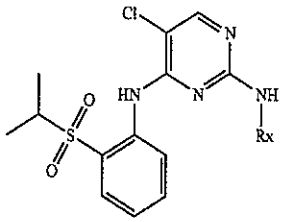
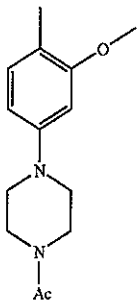
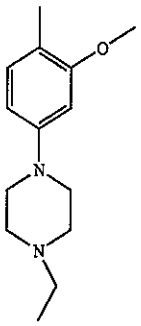
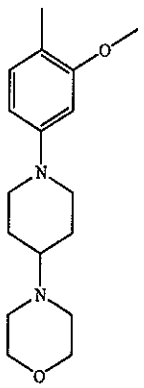


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-11 |  | MS 558 | $CDCl_3$: 1.31(d, 6H), 2.15(s, 3H), 3.12(ddd, 4H), 3.24(sept, 1H), 3.64(t, 2H), 3.80(t, 2H), 3.89(s, 3H), 6.47(dd, 1H), 6.55(d, 1H), 7.29-7.24(m, 1H), 7.33(bs, 1H), 7.62(m, 1H), 7.92(dd, 1H), 8.08(d, 1H), 8.14(s, 1H), 8.60(d, 1H) 9.55(s, 1H) |
| 28-12 |  | MS 544 | $CDCl_3$: 1.16,(t, 3H), 1.31(d, 6H), 2.56-2.44(b, 2H), 2.71-2.60(m, 4H), 3.28-3.17(m, 5H), 3.88(s, 3H), 6.48(dd, 1H), 6.58(d, 1H), 7.30-7.22(m, 1H), 7.63-7.58 (m, 1H), 7.90(dd, 1H), 8.01(d, 1H), 8.12(s, 1H), 8.60(d, 1H) 9.54(s, 1H) |
| 28-13 |  | MS 601 | $CDCl_3$: 1.31(d, 6H, J=6.55), 1.75-1.63(m, 2H), 2.00-1.91 (m, 2H), 2.37-2.27(m, 1H), 2.60(t, 4H, J=4.79), 2.74-2.59(m, 2H), 3.24(sept, 1H), 3.66(d, 2H, J=12.1), 3.75(t, 4H, J=4.53), 3.88(s, 3H), 6.48(dd, 1H, J=2.52, 8.56), 6.56(d, 1H, J=2.52), 7.33-7.22(m, 1H), 7.64-7.59(m, 1H), 7.91(dd, 1H, J=8.05, 1.51), 8.01(d, 1H, J=8.56), 8.12(s, 1H), 8.61(d, 1H, J=7.55) 9.54(s, 1H) |

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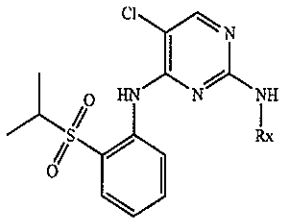
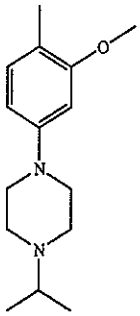
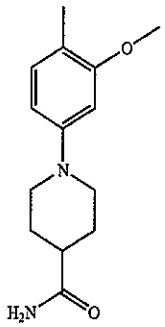
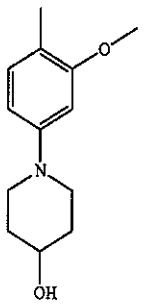
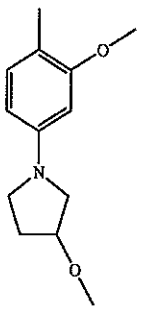


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-14 |  | MS 559 | $CDCl_3$: 1.11(d, 6H, J=6.55), 1.31(d, 6H, J=7.05), 2.82-2.68(m, 5H), 3.20-3.17(m, 4H), 3.28-3.17(m, 1H), 3.87(s, 3H), 6.48(dd, 1H, J=2.52, 8.56), 6.56(d, 1H, J=2.52), 7.33-7.24(m, 1H), 7.62-7.58(m, 1H), 7.90(dd, 1H, J=), 8.01(d, 1H, J=8.56), 8.12(s, 1H), 8.60(d, 1H, J=8.56) 9.54(s, 1H) |
| 28-15 |  | MS 559 | $CDCl_3$: 1.31(d, 6H, J=7.05), 1.97-1.85(m, 2H), 2.17-1.98 (m, 2H), 2.35-2.25(m, 1H), 2.75(m, 2H), 3.24(sept, 1H), 3.65(d, 2H), 3.88(s, 3H), 5.30(bs, 1H), 5.48(bs, 1H), 6.48(dd, 1H, J=2.51, 8.56), 6.56(d, 1H, J=2.52), 7.33-7.21(m, 1H), 7.62(m, 1H), 7.91(dd, 1H, J=1.51, 8.06), 8.03(dd, 1H, J=3.02, 8.56), 8.13(s, 1H), 8.60(d, 1H, J=8.57), 9.54(s, 1H) |
| 28-16 |  | MS 532 | $CDCl_3$: 1.31(d, 6H, J=7.06), 1.46-1.43(m, 1H), 1.79-1.68 (m, 2H), 2.08-1.99(m, 2H), 2.99-2.88(m, 2H), 3.24(sept, 1H), 3.51-3.45(m, 2H), 3.91-3.80(m, 1H), 3.88(s, 3H), 6.49(dd, 1H, J=2.52, 8.56), 6.57(d, 1H, J=2.52), 7.34-7.23(m, 1H), 7.64-7.60(m, 1H), 7.91(dd, 1H, J=1.51, 8.06), 8.02(dd, 1H, J=3.02, 9.06), 8.13(s, 1H), 8.60(d, 1H, J=8.06) 9.53(s, 1H) |
| 28-17 |  | MS 532 | $CDCl_3$: 1.31(d, 6H, J=6.96), 2.18-2.12(m, 2H), 3.24(sept, 1H), 3.37-3.32(m, 2H), 3.39(s, 3H), 3.43(d, 1H, J=8.56), 3.51(dd, 1H, J=5.04, 10.6), 3.87(s, 3H), 4.17-4.09(m, 1H) 6.13(dd, 1H, J=2.51, 8.56),6.16(d, 1H, J=2.52), 7.09(bs, 1H), 7.31-7.21(m, 1H), 7.60-7.56(m, 1H), 7.85(d, 1H, J=8.56), 7.89(dd, 1H, J=1.51, 8.06), 8.10(s, 1H), 8.65(d, 1H, J=9.06) 9.54(s, 1H) |

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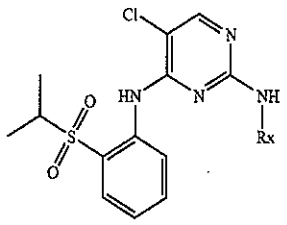
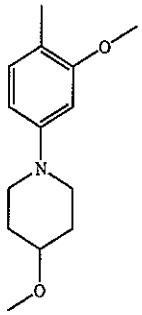
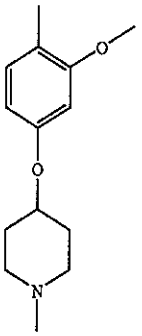
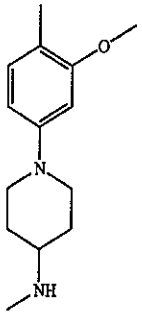


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-18 |  | MS 546 | $CDCl_3$: 1.31(d, 6H, J=7.05), 1.82-1.70(m, 2H), 2.08-1.99 (m, 2H), 2.96-2.87(m, 2H), 3.24(sept, 1H), 3.41-3.33 (m, 1H), 3.40(s, 3H), 3.51-3.42(m, 2H), 3.87(s, 3H), 6.49(dd, 1H, J=2.52, 9.07), 6.57(d, 1H, J=2.52), 7.32-7.22(m, 1H), 7.64-7.60(m, 1H), 7.91(dd, 1H,), 8.00(dd, 1H, J=3.02, 9.06), 8.12(s, 1H), 8.60(d, 1H, J=8.56) 9.53(s, 1H) |
| 28-19 |  | 0.33 (AcOEt) | $CDCl_3$: 1.31(d, 6H, J=7.05), 1.82-1.70(m, 2H), 2.08-1.99 (m, 2H), 2.96-2.87(m, 2H), 3.24(sept, 1H), 3.41-3.33 (m, 1H), 3.40(s, 3H), 3.51-3.42(m, 2H), 3.87(s, 3H), 6.49(dd, 1H, J=2.52, 9.07), 6.57(d, 1H, J=2.52), 7.32-7.22(m, 1H), 7.62(m, 1H), 7.91(dd, 1H,), 8.00(dd, 1H, J=3.02, 9.06), 8.12(s, 1H), 8.60(d, 1H, J=8.56) 9.53(s, 1H) |
| 28-20 |  | MS 544 | $CDCl_3$: 1.31(d, 6H), 1.66-1.53(m, 2H), 2.10-2.01(m, 2H), 2.51(s, 3H), 2.70-2.13(m, 1H), 2.83-2.74(m, 2H), 3.24(Sept, 1H), 3.63-3.55(m, 2H), 3.87(s, 3H), 4.34-4.25 (m, 1H), 6.48(dd, 1H), 6.56(d, 1H), 7.34-7.24(m, 1H), 7.64-7.60(m, 1H), 7.90(dd, 1H), 8.00(d, 1H), 8.12(s, 1H), 8.60(dd, 1H), 9.53(s, 1H) |

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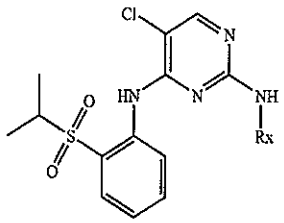
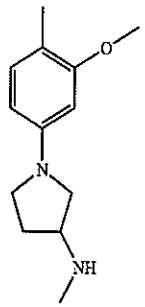
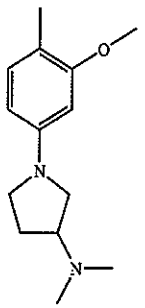
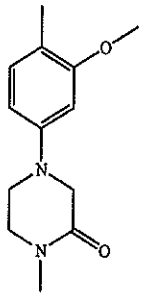


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-21 |  | MS 531 | $CDCl_3$: 1.30(s, 3H), 1.32(s, 3H), 2.33-2.22(m, 1H), 2.54(s, 3H), 3.37-3.20(m, 3H), 3.57-3.44(m, 3H), 3.86(s, 3H), 6.12(dd, 1H), 6.16(d, 1H), 7.14-7.08(m, 1H), 7.30-7.20(m, 1H), 7.65-7.58(m, 1H), 7.93-7.87(m, 1H,), 8.10(s, 1H), 8.64(d, 1H) 9.54(s, 1H) |
| 28-22 |  | MS 545 | $CDCl_3$: 1.30(s, 3H), 1.32(s, 3H), 2.03-1.89(m, 1H), 2.30-2.18(m, 1H), 2.34(s, 6H), 2.96-2.83(m, 1H), 3.29-3.16(m, 2H), 3.40-3.34(m, 1H), 3.53-3.43(m, 2H), 3.87(s, 3H), 6.11(dd, 1H,) 6.13(dd, 1H), 7.08(bs, 1H), 7.31-7.21(m, 1H), 7.60-7.56(m, 1H), 7.85(d, 1H), 7.89(dd, 1H), 8.10(s, 1H), 8.66(d, 1H) 9.54(s, 1H) |
| 28-23 |  | MS 545 | $CDCl_3$: 1.31(s, 3H), 1.32(s, 3H), 3.05(s, 3H), 3.24(sept, 1H), 3.50-3.43(m, 4H), 3.85(s, 2H), 3.89(s, 3H), 6.11(dd, 1H,) 6.43(dd, 1H), 6.50(d, 1H), 7.31-7.28 (m, 1H), 7.64-7.60(m, 1H), 7.92(dd, 1H), 8.09(d, 1H), 8.13(s, 1H), 8.58(d, 1H) 9.55(s, 1H) |

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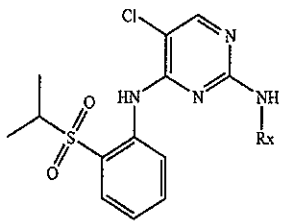
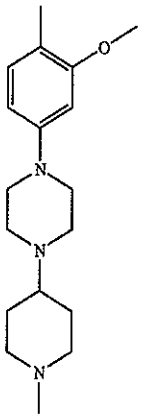
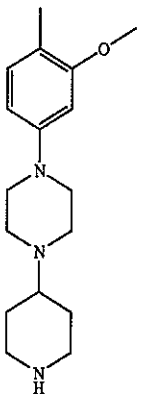
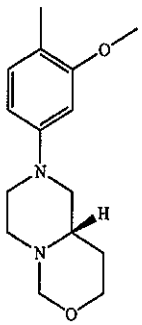


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-24 |  | 0.05 (AcOEt/ MeOH = 4/1) | $CDCl_3$: 1.30(s, 3H), 1.32(s, 3H), 1.92-1.83(m, 1H), 2.17-1.95(m, 1H), 2.43-2.27(m, 2H), 2.79-2.71(m, 4H), 3.15-2.97(m, 4H), 3.23-3.16(m, 4H), 3.24(sept, 1H), 3.87(s, 3H), 6.11(dd, 1H,) 6.47(dd, 1H), 6.55(d, 1H), 7.33-7.23(m, 1H), 7.63-7.59(m, 1H), 7.95(dd, 1H), 8.01(dd, 1H), 8.12(s, 1H), 8.60(d, 1H) 9.54(s, 1H) |
| 28-25 |  | MS 600 | $CDCl_3$: 1.30(s, 3H), 1.32(s, 3H), 1.80-1.70(m, 2H), 2.01-1.93(m, 2H), 2.49-2.28(m, 12H), 2.76-2.62 (m, 4H), 3.04-2.96(m, 4H), 3.16-3.05(m, 2H), 3.24(sept, 1H), 3.72-3.63(m, 2H), 3.87(s, 3H), 6.48(dd, 1H), 6.55(d, 1H), 7.31-7.23(m, 1H), 7.66-7.589 (m, 1H), 7.91(dd, 1H), 8.01(d, 1H), 8.12(s, 1H), 8.60(d, 1H) 9.53(s, 1H) |
| 28-26 |  | MS 573 | $CDCl_3$: 1.30(s, 3H), 1.32(s, 3H), 2.59-2.43(m, 4H), 2.78-2.73(m, 1H), 3.00-2.86(m, 2H), 3.38-3.20(m, 3H), 3.54-2.45(m, 1H), 3.73(dd, 1H), 3.84-3.77(m, 1H), 3.94-3.87(m, 1H), 3.88(s, 3H), 6.46(dd, 1H), 6.53(d, 1H), 7.32-7.23(m, 1H), 7.31(bs, 1H), 7.63-7.52(m, 1H), 7.91(dd, 1H), 8.04(d, 1H), 8.13(s, 1H), 8.60(d, 1H) 9.54(s, 1H) |

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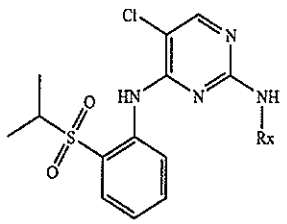
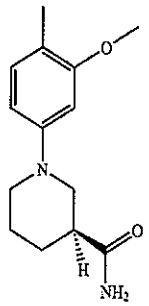
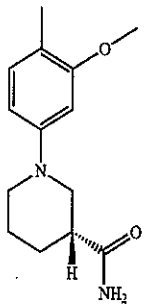
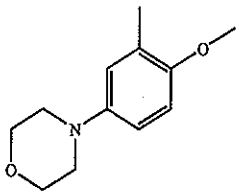
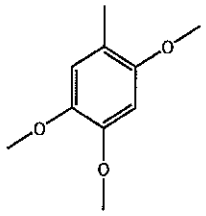
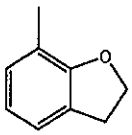
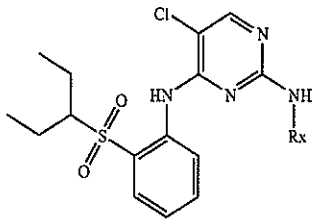
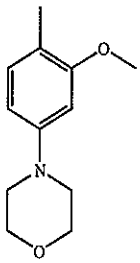
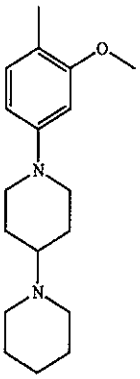
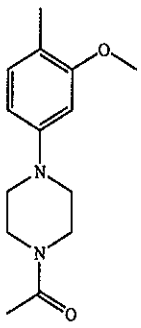
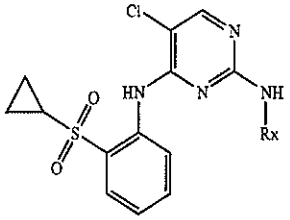
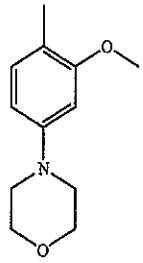
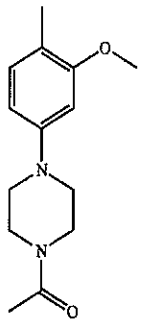
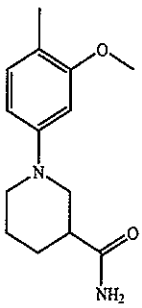


| Expl No. | Rx | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) or Retention time min. (HPLC) |
|---|---|---|---|
| 28-27 |  | MS 559 | $CDCl_3$: 1.30(s, 3H), 1.32(s, 3H), 1.82-1.73(m, 1H), 1.97-1.84(m, 3H), 2.73-2.51(m, 1H), 3.12(t, 2H), 3.31-3.20(m, 3H), 3.90(s, 3H), 5.46-5.37(m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.68-6.62(m, 1H), 7.28-7.21 (m, 1H), 7.33(bs, 1H), 7.65-7.61(m, 1H), 7.92(dd, 1H), 8.08(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.55(s, 1H) |
| 28-28 |  | MS 559 | $CDCl_3$: 1.30(s, 3H), 1.32(s, 3H), 1.82-1.73(m, 1H), 1.97-1.84(m, 3H), 2.73-2.51(m, 1H), 3.12(t, 2H), 3.31-3.20(m, 3H), 3.90(s, 3H), 5.46-5.37(m, 1H), 6.53(dd, 1H), 6.59(d, 1H), 6.68-6.62(m, 1H), 7.28-7.21 (m, 1H), 7.33(bs, 1H), 7.65-7.61(m, 1H), 7.92(dd, 1H), 8.08(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.55(s, 1H) |
| 28-29 |  | MS 413 | $CDCl_3$: 1.31(s, 3H), 1.33(s, 3H), 2.92(t, 4H), 3.28(sept, 1H) 3.73(t, 4H), 3.87(s, 3H), 6.51(dd, 1H), 6.82(d, 1H), 7.32-7.23(m, 1H), 7.57(bs, 1H), 7.70-7.64 (m, 1H), 7.92(dd, 1H), 8.01(bs, 1H), 8.12(s, 1H), 8.60(d, 1H), 9.53(s, 1H) |
| 28-30 |  | MS 493 | $CDCl_3$: 1.30(s, 3H), 1.33(s, 3H), 3.25(sept, 1H) 3.60 (bs, 3H), 3.89(s, 3H), 6.59(s, 1H), 7.27-7.18(m, 1H), 7.61(dd, 1H), 7.83(bs, 1H), 7.90(dd, 1H), 8.15 (s, 1H), 8.55(d, 1H), 9.55(s, 1H) |
| 28-31 |  | MS 445 | $CDCl_3$: 1.31(d, 6H), 1.59-1.37(m, 2H), 1.81-1.69(m, 1H), 1.87(d, 2H), 2.73-2.67(m, 2H), 3.28-3.21(m, 1H), 3.37(s, 3H), 3.61(d, 1H), 3.87(s, 3H), 6.49(dd, 1H), 7.025(bs, 1H), 7.28-7.23(m, 1H), 7.64-7.59(m, 1H), 7.93-7.89(m, 2H), 8.15(s, 1H), 8.57(dd, 1H) 9.56(s, 1H) |



| Expl No. | Rx | HPLC Retention time (min) | Mass (ESI) m/z |
|---|---|---|---|
| 29-1 |  | 3.30 | 546 (M + H) |
| 29-2 |  | 2.82 | 627 (M + H) |
| 29-3 |  | 3.07 | 587 (M + H) |



| Expl No. | Rx | HPLC Retention time (min) | Mass (ESI) m/z |
|---|---|---|---|
| 30-1 |  | 2.82 | 516 (M + H) |
| 30-2 |  | 2.65 | 557 (M + H) |
| 30-3 |  | 2.50 | 557 (M + H) |

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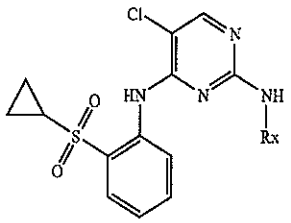
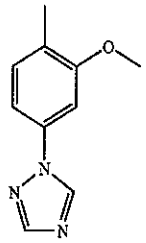
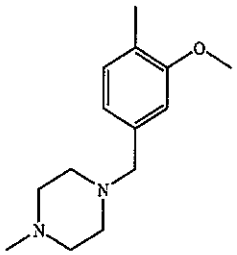
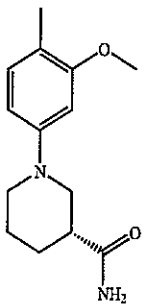


| Expl No. | Rx | HPLC Retention time (min) | Mass (ESI) m/z |
|---|---|---|---|
| 30-4 |  | 3.10 | 498 (M + H) |
| 30-5 |  | 2.30 | 543 (M + H) |
| 30-6 |  | 2.52 | 557 (M + H) |

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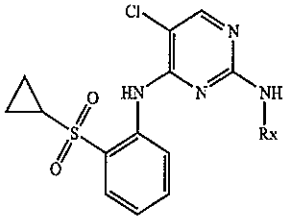
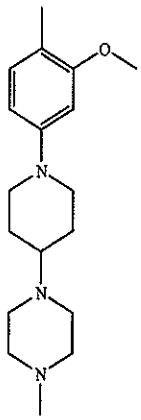
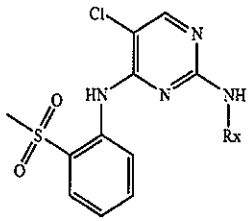
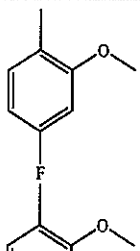
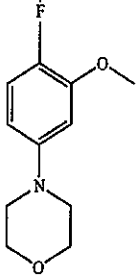
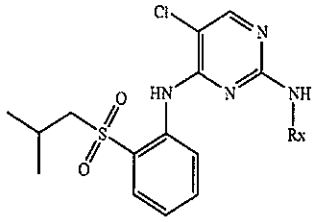
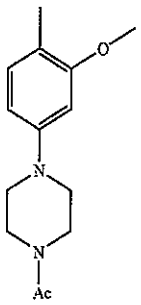
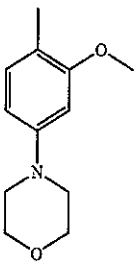


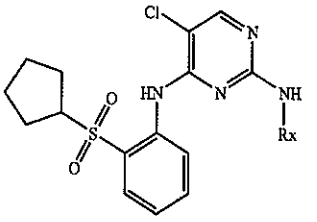
| Expl No. | Rx | HPLC Retention time (min) | Mass (ESI) m/z |
|---|---|---|---|
| 30-7 |  | 2.23 | 612 (M + H) |

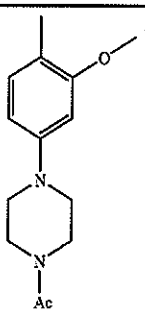


| Expl No. | Rx | HPLC Retention time (min) | Mass (ESI) m/z |
|---|---|---|---|
| 31-1 |  | 3.15 | 423 (M + H) |
| 31-2 |  | 2.62 | 490 (M + H) |

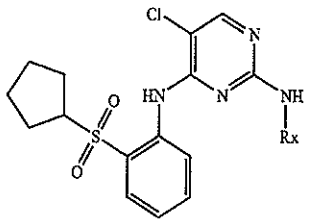


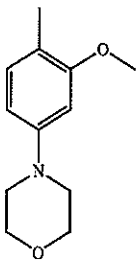
| Expl No. | Rx | MS | NMR (400 MHz) in $CDCl_3$, δ (ppm) |
|---|---|---|---|
| 32-1 |  | 585.3 | 1.03(s, 3H), 1.04(s, 3H), 2.15(s, 3H), 2.32(sept, 1H) 3.00(d, 2H) 3.10(t, 2H), 3.13(t, 2H), 3.64(t, 2H), 3.79(t, 2H), 3.89(s, 3H), 6.45(dd, 1H), 6.55(d, 1H), 7.34-7.26 (m, 1H), 7.52(bs, 1H), 7.64-7.60(m, 1H), 7.97(dd, 1H), 8.07(d, 1H), 8.15(s, 1H), 8.54(d, 1H), 9.32(s, 1H) |
| 32-2 |  | 532 (M + H) | 3.17 |

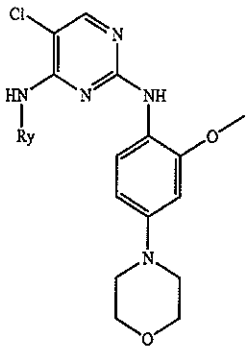


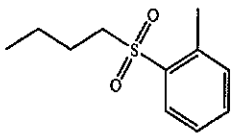
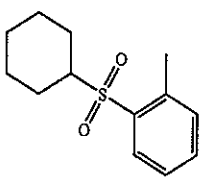
| Expl No. | Rx | MS | NMR (400 MHz) in $CDCl_3$, δ (ppm) |
|---|---|---|---|
| 33-1 |  | 585.3 | 1.66-1.52(m, 2H), 1.92-1.73(m, 4H), 2.12-2.03(m, 2H), 2.15(s, 3H), 3.00(d, 2H) 3.11(t, 2H), 3.14(t, 2H), 3.58-3.46(m, 1H), 3.64(t, 2H), 3.80(t, 2H), 3.89(s, 3H), 6.48(dd, 1H), 6.55(d, 1H), 7.30-7.24(m, 1H), 7.52(bs, 1H), 7.63-7.58(m, 1H), 7.94(dd, 1H), 8.08(d, 1H), 8.14(s, 1H), 8.60(d, 1H), 9.54(s, 1H) |

-continued

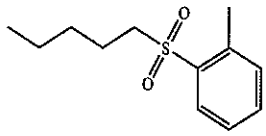
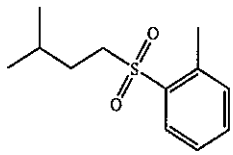
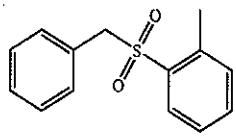
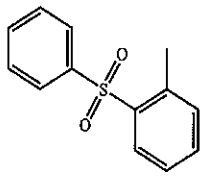


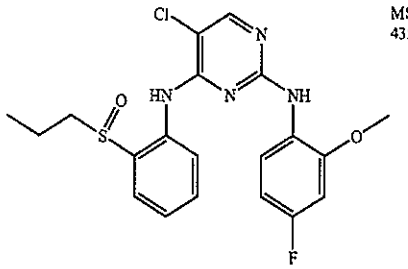
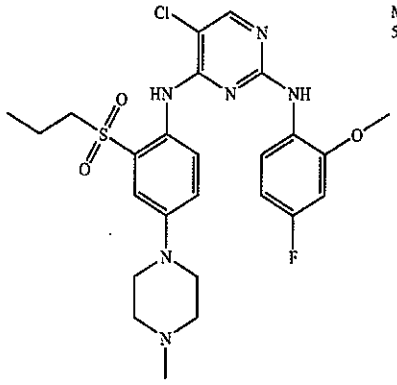
| Expl No. | Rx | MS | NMR (400 MHz) in $CDCl_3$, δ (ppm) |
|---|---|---|---|
| 33-2 |  | 544 (M + H) | 3.15 |

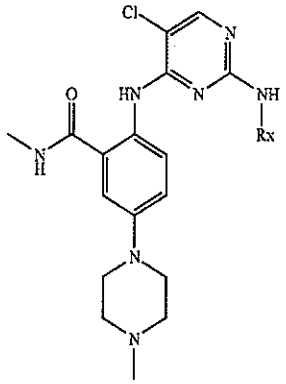


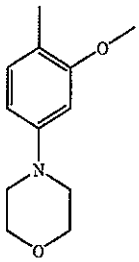
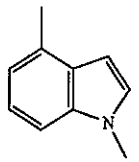
| Expl No. | Rx | HPLC Retention time (min) | Mass (ESI) m/z |
|---|---|---|---|
| 34-1 |  | 3.15 | 532 (M + H) |
| 34-2 |  | 3.34 | 558 (M + H) |

-continued

| | | | |
|---|---|---|---|
| 34-3 |  | 3.35 | 546 (M + H) |
| 34-4 |  | 3.32 | 546 (M + H) |
| 34-5 |  | 3.09 | 566 (M + H) |
| 34-6 |  | 2.87 | 552 (M + H) |

| Ex No | | MS | NMR (400 MHz), $CDCl_3$, δ ppm |
|---|---|---|---|
| 34-7 |  | MS 435, 436 | 1.05(t, 3H), 1.69-1.78(m, 2H), 2.86-2.95(m, 1H), 3.16-3.25(m, 1H), 6.57-6.68(m, 2H), 7.17(dd, 1H), 7.35-7.39(m, 1H), 7.50(dd, 1H), 8.13(s, 1H), 8.16-8.21 (m, 1H), 8.48(d, 1H), 10.14(s, 1H) |
| 34-8 |  | MS 549, 551 | 0.94(t, 3H), 1.69-1.80(m, 2H), 2.38(s, 3H), 2.55-2.64 (m, 4H), 3.02-3.08(m, 2H), 3.22-3.29(m, 4H), 3.88(s, 3H), 6.55(ddd, 1H), 6.60-6.66(m, 1H), 7.13-7.18(m, 1H), 7.34(br.s, 1H), 7.44(d, 1H), 8.10(s, 1H), 8.10-8.23 (m, 2H), 8.88(s, 1H). |

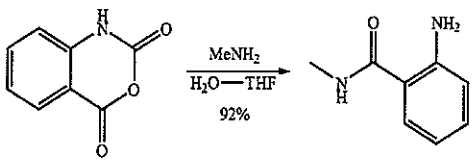


| | | | |
|---|---|---|---|
| 35-1 |  | 567 [M + 1]+ | DMSO-d6: 2.24(s, 3H), 2.45-2.50(m, 4H), 2.78(d, 3H), 3.10-3.17(m, 8H), 3.74-3.79(m, 7H), 6.49(dd, 1H), 6.66(d, 1H), 6.85-6.89(m, 1H), 7.18(d, 1H), 7.40(d, 1H), 7.98-8.02(m, 2H), 8.29(br.d, 1H), 8.60-8.66 (m, 1H), 11.17(s, 1H). |
| 35-2 |  | 505 {M + 1}+ | DMSO-d6: 2.24(s, 3H), 2.46-2.50(m, 4H), 2.79(d, 3H), 3.13-3.17(m, 4H), 3.78(s, 3H), 6.69(d, 1H), 6.87(dd, 1H), 7.07-7.17(m, 2H), 7.19-7.23(m, 2H), 7.54(d, 1H), 8.13(s, 1H), 8.45(s, 1H), 8.65-8.75(m, 1H), 9.04(s, 1H), 11.19(s, 1H) |

Example 36

Intermediates for Left Anilines

36-1 Preparation of 2-amino-N-methyl-benzamide

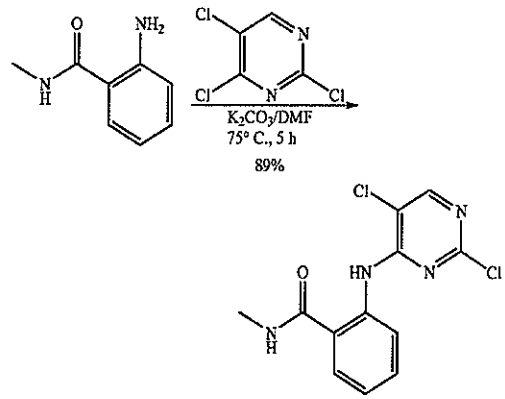



To a suspension of 16.3 g (100 mmol) of isatoic anhydride in 100 mL of $H_2O$ is added portionwise 100 mL of 2N methylamine-tetrahydrofuran solution (200 mmol) at room temperature. The reaction mixture is stirred for 1 hour and then extracted with AcOEt. The organic layer is washed with $H_2O$ and brine, dried over $Na_2SO_4$, and concentrated under reduced pressure to give 13.79 g of desired product, 2-amino-N-methyl-benzamide (92 mmol, 92%) as colorless solid.

NMR (400 MHz, CDCl3, δ): 2.97 (d, 3H, J=4.52 Hz), 5.49 (bs, 1H), 6.07 (bs, 1H), 6.64 (ddd, 1H, J=8.04, 7.56, 1.0 Hz), 6.68 (dd, 1H, J=8.32, 1.0 Hz), 7.20 (ddd, 1H, J=8.32, 7.56, 1.52 Hz), 7.29 (dd, 1H, J=8.04, 1.52 Hz).

36-2

2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-methyl-benzamide




To a solution of 15.0 g (99.8 mmol) of 2-amino-N-methyl-benzamide in DMF (300 mL) are added 2,4,5-trichloropyrimidine (23.8 g, 130 mmol) and potassium carbonate (17.9 g, 130 mmol). The reaction mixture is stirred at 75° C. for 5 hours, cooled to room temperature, and then poured into $H_2O$

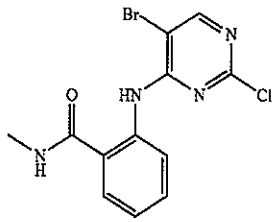
(600 mL). The resulting precipitate is collected by a filtration followed by washing with 50% aqueous $CH_3CN$ (200 mL) and dried under reduced pressure (40° C., 10 hours) to give desired 2-(2,5-dichloro-pyrimidin-4-yl-amino)-N-methyl-benzamide as ivory solid (26.4 g, 88.9 mmol, 89%).

NMR (400 MHz, DMSO-d6, δ): 2.81 (d, 3H, J=4.52 Hz), 7.22 (dd, 1H, J=8.56, 8.04 Hz), 7.60 (ddd, 1H, J=8.56, 8.56, 1.0 Hz), 7.81 (dd, 1H, J=8.04, 1.0 Hz), 8.48 (s, 1H), 8.52 (d, 1H, J=8.56 Hz) 8.80-8.90 (m, 1H), 12.18 (s, 1H).

According the manner described above, the following compounds are prepared.

36-3

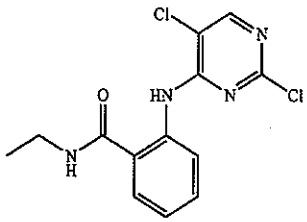
2-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl-benzamide



NMR (400 MHz, DMSO-$d_6$, δ): 2.81(d, 3H), 7.23(ddd, 1H, J=7.54, 7.54, 1.0 Hz), 7.59(ddd, 1H, J=7.93, 8.06, 1.52 Hz),7.79(dd, 1H, J=7.8, 1.52 Hz), 8.47(dd, 1H J=8.06, 1.0 Hz), 8.55(s, 1H), 8.81-8.87(m, 1H), 12.0(brs, 1H). Rf: 0.46 (n-Hexane:AcOEt=7:3).

36-4

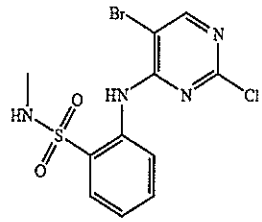
2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-ethyl-benzamide



NMR (400 MHz, $CDCl_3$, δ): 1.28 (t, d=7.04, 3H), 3.48-3.57 (m, 2H), 6.22 (br. s, 1H), 7.11-7.17 (m, 1H), 7.51 (dd, J=1.0, 8.04, 1H), 7.53-7.61 (m, 1H), 8.22 (s, 1H), 8.69-8.74 (m, 1H), 11.66 (br. s, 1H). Rf: 0.60 (Hexane:AcOEt=1:1).

36-5

Preparation of 2-(5-bromo-2-chloro-pyrimidin-4-ylamino)-N-methyl -benzenesulfonamide



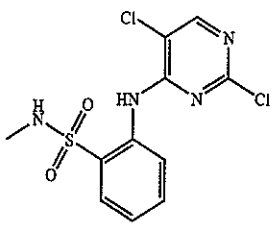
A suspension of 5-bromo-2,4-dichloropyrimidine (684 mg, 3.0 mmol) and 2-amino-N-methyl-benzenesulfonamide (559 mg, 3.0 mmol) in N,N-dimethylformamide (10 mL) containing potassium carbonate (830 mg, 6.0 mmol) is stirred at room temperature for 23 hours. Saturated aqueous ammonium chloride is added and the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by silica gel column chromatography (n-hexane-ethyl acetate gradient) to afford the title compound as a slightly yellow solid.

$^1$H-NMR ($CDCl_3$), δ(ppm): 2.67 (d, 3H), 4.79 (q, 1H), 7.26 (s, 1H), 7.29 (ddd, 1H), 7.66 (ddd, 1H), 7.95 (dd, 1H), 8.37 (s, 1H), 8.48 (d, 1H), 9.52 (s, 1H). Rf (n-hexane:ethyl acetate=10:3): 0.33.

According to the manner described above, the following compound is prepared.

36-6

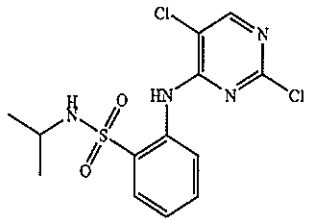
2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-methyl-benzenesulfonamide



$^1$H-NMR (400 MHz, $CDCl_3$, δ);2.67(d, 3H),4.97-5.04(m, 1H), 7.29(ddd, 1H, J=7.54, 7.54, 1.0 Hz), 7.66(ddd, 1H, J=7.93, 8.08, 1.48 Hz),7.94(dd, 1H, J=8.04, 1.52 Hz), 8.24(s, 1H), 8.51(dd, 1H J=8.06, 1.0 Hz), 9.64(brs, 1H). Rf: 0.45 (n-Hexane:AcOEt=4:1).

36-7

2-(2,5-Dichloro-pyrimidin-4-ylamino)-N-isopropyl-benzenesulfonamide



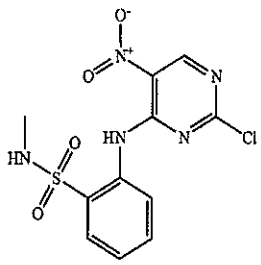
To a solution of 2-amino-N-isopropyl-benzenesulfonamide (16.1 g, 75.1 mmol) in DMI (150 mL) is added sodium hydride (6.6 g, 165.3 mmol) portionwise at 0° C. After the mixture is stirred at room temperature for one hour, 2,4,5-trichloropyrimidine (20.7 g, 112.7 mmol) is added at 0° C. After further stirring at room temperature for 5 hrs, water is added and the mixture is extracted with AcOEt three times. Organic layer is washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue is purified by silica gel column chromatography (Hexane to Hexane:AcOEt=4:1) to afford the title compound as pale brown solid (10.2 g, 38%).

$^1$H-NMR (400 MHz, $CDCl_3$, δ);1.06(d, 6H), 3.43-3.53(m, 1H), 4.38(d, 1H), 7.29(dd, 1H), 7.66(dd, 1H), 7.98(d, 1H), 8.29(s, 1H), 8.51 (d, 1H), 9.51 (brs, 1H). Rf: 0.45 (n-Hexane: AcOEt=4:1)

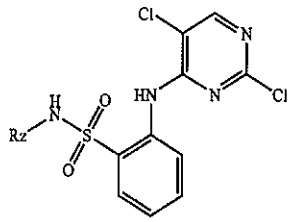
The following compounds are prepared in the same manner described above.

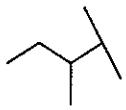
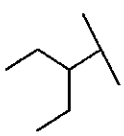
36-10

Preparation of 2-(2-chloro-5-nitro-pyrimidin-4-ylamino)-N-methyl -benzenesulfonamide



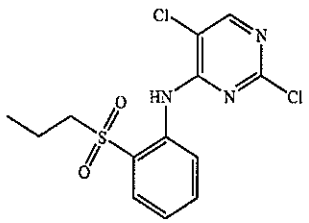
2,4-Dichloro-5-nitro-pyrimidine (1.94 g, 10 mmol) and 2-amino-N -methyl-benzenesulfonamide (1.86 g, 10 mmol) are dissolved in $CHCl_3$ (30 mL). The reaction mixture is heated at 61° C. for 2 h. The solvent is evaporated and the residue is washed with ether to give the title product. Rf=0.5 (n-hexane:ethyl acetate=1:1). $^1$H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.67 (d, 3H), 4.6-4.7 (m, 2H), 7.41 (t 1H), 7.7 (t, 1H), 8.04 (d, 1H), 8.15 (d, 1H), 9.21 (s, 1H), 11.2 (s, 1H).



| Expl No. | Rz | Rf (solvent) or MS | NMR (400 MHz), δ (ppm) |
|---|---|---|---|
| 36-8 |  | 0.45 (n-Hexane:AcOEt = 4:1) | DMSO-$d_6$: 0.63(t, 6H), 0.86(d, 3H), 1.21-1.31(m, 2H), 3.02-3.12(m, 1H), 7.37(dd, 1H), 7.71(dd, 1H), 7.85(d, 1H), 7.89(d, 1H), 8.20(d, 1H), 8.56(s, 1H), 9.51(brs, 1H) |
| 36-9 |  | 0.46 (n-Hexane:AcOEt = 7:3) | $CDCl_3$; 0.70(t, 6H), 1.23-1.45(m, 4H), 3.03-3.13(m, 1H), 4.27(d, 1H), 7.27(dd, 1H), 7.65(dd, 1H), 7.98(d, 1H), 8.29(s, 1H), 8.52(d, 1H), 9.59(brs, 1H) |

36-11

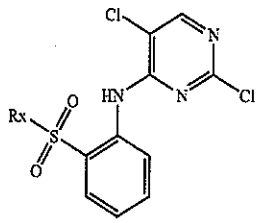
Preparation of (2,5-Dichloro-pyrimidin-4-yl)-[2-(propane-1-sulfonyl)-phenyl]-amine

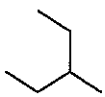


To a solution of 2-(Propane-1-sulfonyl)-phenylamine (3.69 g, 18.5 mmol) of N,N-dimethylformamide (40 mL), sodium hydride (1.48 g, 37 mmol) is added portionwise at 0° C. After stirring, 2,4,5-trichloropyrimidine (2.1 mL, 18.5 mmol) is added. The mixture is stirred at 0° C. for 30 minutes and is further stirred at room temperature for 7 hrs. After adding saturated aqueous ammonium chloride, the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by silica gel column chromatography (n-hexane-ethyl acetate gradient) to afford the title compound as colorless solids.

$^1$H-NMR ($CDCl_3$), δ (ppm): 0.99 (t, 3H), 1.77 (d, 2H), 3.07-3.11 (m, 2H), 7.26 (s, 1H), 7.32 (ddd, 1H), 7.73 (ddd, 1H), 7.95 (dd, 1H), 8.31 (s, 1H), 8.61 (dd, 1H), 9.94 (bs, 1H). Rf (n-hexane ethyl acetate=3:1): 0.63

According to the manner described above, the following compounds are prepared.



| Expl No. | Rx | Identification |
|---|---|---|
| 36-12 |  | $^1$H-NMR($CDCl_3$), δ(ppm): 1.35(d, 6H), 3.18-3.24(m, 1H), 7.30-7.34(m, 1H), 7.70-7.75(m, 1H), 7.92(dd, 1H), 8.30(s, 1H), 8.63(d, 1H), 10.06(s, 1H). Rf 0.70:(AcOEt) |
| 36-13 |  | NMR(400 MHz) in $CDCl_3$, δ(ppm): 1.29(t, 3H), 3.15(q, 1H), 7.31-7.35(m, 1H), 7.71-7.75(m, 1H), 7.96(dd, 1H), 8.31(s, 1H), 8.60(d, 1H), 9.92(s, 1H). Rf: 0.67 (AcOEt). |
| 36-14 |  | 1.01-1.06(m, 2H), 1.32-1.37(m, 2H), 2.49-2.55(m, 1H), 7.29-7.33(m, 1H), 7.69-7.73(m, 1H), 7.91(dd, 1H), 8.31(s, 1H), 8.58(d, 1H), 9.90(s, 1H). Rf 0.69 (AcOEt) |
| 36-15 |  | 0.99(t, 6H), 1.72-1.90(m, 4H), 2.76-2.82(m, 1H), 7.26-7.34 (m, 1H), 7.69-7.74(m, 1H), 7.92(dd, 1H), 8.30(s, 1H), 8.62(d, 1H), 10.02(s, 1H). Rf: 0.73(AcOEt) |

Example 36-16

Synthesis of substituted amines which are commercially not available:

Preparation of 3-amino-4'-methoxy-4-methylbiphenyl

To a solution of 4-methoxyphenyl-boronic acid (500 mg, 3.29 mmol) in toluene (5.2 mL) and ethanol (1.3 mL), potassium carbonate (910 mg, 6.58 mmol), tetrakis(triphenylphosphine) palladium (228.1 mg, 0.099 mmol) and 4-bromo-1-methyl-2-nitrobenzene (711 mg, 3.29 mmol) are added and stirred at 100° C. for 7 hours. The mixture is poured into water and extracted with ethyl acetate two times. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane:ethyl acetate=5:1) to afford the 4'-methoxy-4-methyl-3-nitro-biphenyl as a yellow solid.

$^1$H-NMR (δ, ppm): 2.62 (s, 3H), 3.86 (s, 3H), 7.02-6.98 (m, 2H), 7.37 (d, 1H), 7.54 (dd, 2H), 7.68 (dd, 1H), 8.18 (d, 1H). Rf (hexane:ethyl acetate=3:1): 0.40.

A suspension of 4'-methoxy-4-methyl-3-nitrobiphenyl (630 mg, 2.95 mmol) and 10% palladium on charcoal (63 mg, 0.059 mmol) in methanol (6 mL) is stirred under hydrogen atmosphere for 12 hours. Palladium catalyst is removed by filtration and the resulting solution is evaporated in vacuo to afford the title compound.

$^1$H-NMR (δ, ppm): 2.20 (s, 3H), 3.84 (s, 3H), 6.87 (d, 1H), 6.89 (dd, 1H), 6.95 (d, 2H), 7.09 (d, 1H), 7.48 (d, 2H). Rf (n-hexane:ethyl acetate=1:1): 0.50.

Preparation of 4-(3-amino-4-methylbenzoyl)-piperazine-1-carboxylic acid tert-butyl ester

To a solution of 4-methyl-3-nitro-benzoic acid (300 mg, 2.76 mmol), N -butoxycarbonyl-piperazine (340 mg, 1.83 mmol) in DMF (3.0 mL), triethylamine (300 μL, 3.59 mmol), TBTU (800 mg, 2.49 mmol) and HOAt (270.5 mg, 1.99 mmol) are added and stirred at room temperature for 24 hours. The mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n -hexane:ethyl acetate=5:1) to afford 4-(4-methyl-3-nitrobenzoyl)-piperazinc-1-carboxylic acid tert-butyl ester as a colorless solid.

$^1$H-NMR (δ, ppm): 1.47 (s, 9H), 2.64 (s, 3H), 3.28-3.88 (m, 8H), 7.42 (d, 1H), 7.56 (dd, 1H), 8.03 (d, 1H). Rf (hexane: ethyl acetate=10:1): 0.13.

The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Preparation of 4-(3-amino-4-methylphenyl)-morpholine

To a solution of 4-bromo-1-methyl-2-nitrobenzene (225 mg, 1.04 mmol), morpholine (125 μL, 1.25 mmol), and cesium carbonate (474.4 mg, 1.46 mmol) in toluene, palladium diacetate (31.2 mg, 0,139 mmol) and 2-(di-t-butylphosphino)biphenyl (125 mg, 0.403 mmol) are added and stirred at 100° C. for 5 hours. After cooling, the mixture is filtered to remove insoluble material. The filtrate is poured into water and extracted with ethyl acetate twice. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane:ethyl acetate=5:1) to afford 4-(4-methyl-3-nitrophenyl)morpholine as a yellow solid.

$^1$H-NMR (δ, ppm): 2.50 (s, 3H), 3.17-3.19 (m, 4H), 3.86-3.88(m, 4H), 7.04 (dd, 1H), 7.21 (d, 1H), 7.47 (d, 1H). Rf (hexane:ethyl acetate=5:1): 0.20.

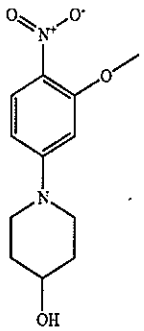
The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Example 37

Synthesis of Substituted Amines Which are Commercially not Available

37-1

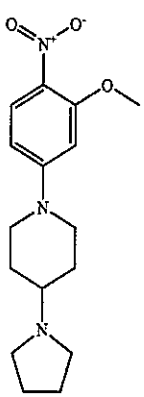
Preparation of 1-(3-Methoxy-4-nitro-phenyl)-piperdin-4-ol



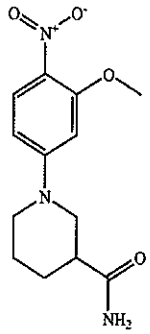
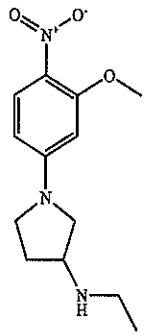
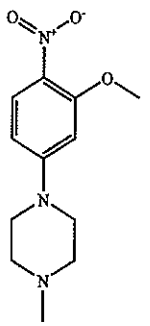
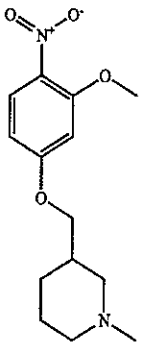
To a suspension of piperidin-4-ol (2.79 g, 28 mmol) and potassium carbonate (3.88 g, 28 mmol) in N,N-dimethylformamide (40 mL), 4-Fluoro-2-methoxy-1-nitro-benzene (4.0 g, 23 mmol) is added and stirred at room temperature for 24 hours. The mixture is poured into water and the precipitate is collected by a filtration. The resulting solid is dried in vacuo at 50° C. to afford 1-(3-methoxy-4-nitro-phenyl)-piperidin-4-ol (5.23 g) as yellow solids in 89% yield.

$^1$H-NMR (400 MHz, $CDCl_3$, δ, ppm):1.54(d, 1H), 1.62-1.71(m, 2H), 1.98-2.04(m, 2H), 3.22(ddd, 4H), 3.73-3.80(m, 2H), 3.95(s, 3H), 3.98-4.02(m, 1H), 6.33(d, 1H), 6.43(dd, 1H), 8.00(d, 1H).

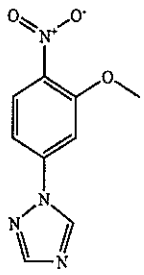
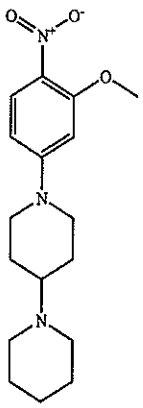
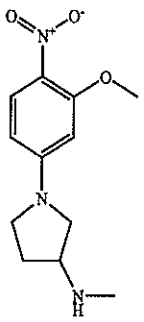
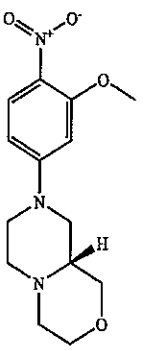
By repeating the procedures described above using appropriate starting materials and conditions the following compounds are obtained.

| Ex-No | Rx | Identification |
|---|---|---|
| 37-2 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.53-1.72(m, 2H), 1.80-1.83 (m, 4H), 1.99-2.04(m, 2H), 2.24-2.31(m, 1H), 2.54-2.67 (m, 4H), 3.03(dt, 2H), 3.84-3.89(m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.01(d, 1H). Rf 0.54(AcOEt) |

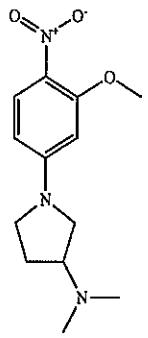
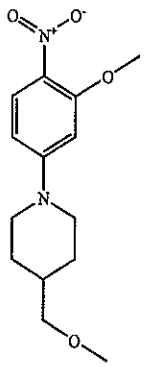
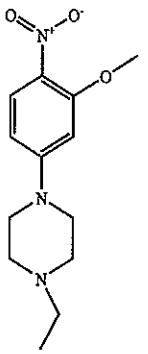
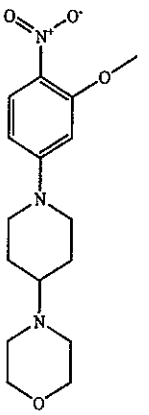
-continued

| Ex-No | Rx | Identification |
|---|---|---|
| 37-3 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.81-1.91(m, 2H), 1.99-2.04 (m, 2H), 2.38-2.48(m, 1H), 3.03(ddd, 2H), 3.91-3.96(m, 2H), 3.95(s, 3H), 5.22-5.41(m, 1H), 5.40-5.53(m, 1H), 6.36(d, 1H), 6.43(dd, 1H), 8.00(d, 1H). Rf 0.15(AcOEt) |
| 37-4 |  Ethyl-[1-(3-methyoxy-4-nitro-phenyl-pyrrolidin-3-yl]-amine | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.15(t, 3H), 1.88-1.96(m, 1H), 2.22-2.30(m, 1H), 2.68-2.77(m, 2H), 3.15-3.18(m, 1H), 3.38-3.44(m, 1H), 3.52-3.62(m, 2H), 3.93(s, 3H), 5.92(d, 1H), 6.07-6.10(m, 1H), 8.00-8.02(m, 1H). Rf 0.65(n-hexane:AcOEt = 1:1). |
| 37-5 |  1-(3-Methoxy-4-nitro-phenyl)-4-methyl-piperazine | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 2.36(s, 3H), 2.52-2.57(m, 4H), 3.40-3.43(m, 4H), 3.95(s, 3H), 6.32(d, 1H, J=2.52 Hz), 6.43(dd, 1H, J=9.56, 2.52 Hz), 7.99(d, 1H, J=9.08 Hz). Rf 0.60 (MeOH:$CH_2Cl_2$ = 4:1). |
| 37-6 |  3-(3-Methoxy-4-nitro-phenoxymethy-1-methyl-piperidine | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.10-1.19(m, 1H), 1.59-2.18 (m, 6H), 2.28(s, 3H), 2.71-2.74(m, 1H), 2.88-2.91(m, 1H), 3.86.-3.95(m, 5H), 6.47-6.52(m, 2H), 7.97-8.00(m, 1H). Rf 0.65(n-hexane:AcOEt = 1:1) |

-continued

| Ex-No | Rx | Identification |
|---|---|---|
| 37-7 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 4.08(s, 3H), 7.30(dd, 1H), 7.58(d, 1H), 8.05(d, 1H), 8.15(s, 1H), 8.67(s, 1H). Rf: 0.42 (AcOEt) |
| 37-8 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.40-1.50(m, 2H), 1.55-1.69 (m, 6H), 1.90-1.96(m. 2H), 2.45-2.53(m, 5H), 2.90-2.99 (m, 2H), 3.90-4.00(m, 2H), 3.94(s, 3H), 6.30(d, 1H, J=, 2.5 Hz), 6.41(dd, 1H, J=9.0, 2.5 Hz), 7.99(d, 1H, J=9.0 Hz) |
| 37-9 |  | $^1$H-NMR(400 MHz, DMSO-d6, δ, ppm): 1.95-1.82(m, 2H), 2.15-2.06(m, 1H), 2.30(s, 3H), 3.17(dd, 1H), 3.32-3.23(m, 1H), 3.56-3.34(m, 3H), 3.96(s, 1H), 6.09(d, 1H), 6.21(dd, 1H), 7.91(d, 1H) |
| 37-10 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 2.30-2.48(m, 3H), 2.59-2.66 (m, 1H), 2.70-2.76(m, 1H), 2.85-2.92(m, 1H), 3.09-3.17 (m, 1H), 3.30 -3.34(m, 1H), 3.52-3.58(m, 1H), 3.68-3.84 (m, 3H), 3.87-3.91(m, 1H), 3.96(s, 3H), 6.32(d, 1H, J=2.5 Hz), 6.42(dd, 1H, J=9.6, 2.5 Hz), 8.00(d, 1H, J=9.6 Hz) |

-continued

| Ex-No | Rx | Identification |
|---|---|---|
| 37-11 |  | $^1$H-NMR(400 MHz, DMSO-d6, $CDCl_3$, δ, ppm): 1.90-1.79(m, 1H), 2.25-2.15(m, 1H), 2.21(s, 3H), 2.87-2.77(m, 1H), 3.16 (dd, 1H), 3.42-3.32(m, 1H), 3.59-3.52(m, 1H), 3.67-3.61(m, 1H), 3.91(s, 3H), 6.13(d, 1H), 6.24(dd, 1H)), 7.91(dd, 1H) |
| 37-12 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.43-1.00(m, 2H), 1.95-1.81(m, 2H), 2.94-2.17(m, 2H), 2.96(s, 3H), 3.27(d, 2H), 3.35(s, 3H), 3.97-3.90(m, 2H), 3.95(s, 3H), 6.30(d, 1H), 6.42(dd, 1H) 8.00(d, 1H). Rf: 0.25 (AcOEt) |
| 37-13 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.14(t, 3H), 2.48(dd, 2H), 2.59(t, 4H), 3.42(t, 4H), 3.95(s, 3H), 6.32(d, 1H), 6.43(dd, 1H) 8.01(d, 1H). Rf 0.15(AcOEt) |
| 37-14 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.02-0.89(m, 2H), 2.01-1.94(m, 2H), 2.52-2.38(m, 1H), 2.65-2.53(m, 4H), 3.04-2.94(m, 2H), 3.79-3.69(m, 4H), 3.97-3.88(m, 2H), 3.95(s, 3H), 6.32(d, 1H), 6.42(dd, 1H) 8.00(d, 1H). Rf 0.10(AcOE |

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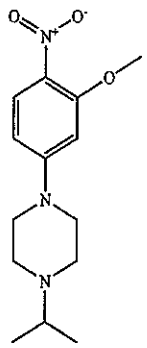
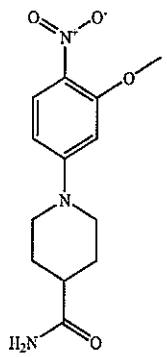
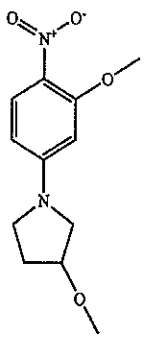
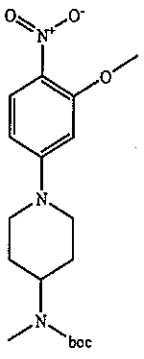
| Ex-No | Rx | Identification |
|---|---|---|
| 37-15 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.08(s, 3H), 1.09(s, 3H), 2.66(t, 4H), 2.74(sept, 1H), 3.41(t, 4H), 3.95(s, 3H), 6.32(d, 1H), 6.42(dd, 1H) 8.00(d, 1H). Rf 0.15(AcOEt) |
| 37-16 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.91-1.81(m, 2H), 2.06-1.97(m, 2H), 2.48-2.40(m, 1H), 3.07-2.98(m, 2H), 3.97-3.93(m, 2H), 3.93(s, 3H), 5.37-5.30(m, 1H), 5.55-5.43(m, 1H), 6.33(d, 1H), 6.43(dd, 1H) 8.00(d, 1H). Rf 0.10(AcOEt) |
| 37-17 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.18-2.07(m, 1H), 2.30-2.22(m, 1H), 3.38(s, 3H), 3.56-3.44(m, 4H), 3.95(s, 3H), 4.13(ddd, 1H), 5.96(d, 1H), 6.12(dd, 1H) 8.03(d, 1H). Rf 0.30(AcOEt) |
| 37-18 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.46(s, 9H), 1.81-1.68(m, 4H), 2.73(bs, 3H), 3.07-2.97(m, 2H), 3.95(s, 3H), 4.03-3.94(m, 2H), 6.32(d, 1H), 6.43(dd, 1H) 8.00(d, 1H). Rf 0.55 (Hexane:AcOEt) |

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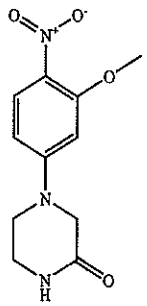
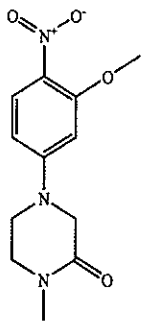
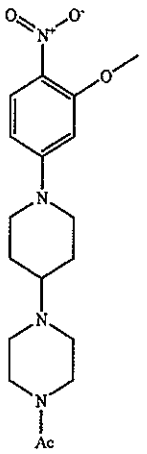
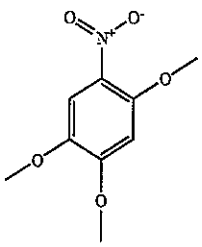
| Ex-No | Rx | Identification |
|---|---|---|
| 37-19 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.60-3.57(m, 2H), 3.68-3.65(m, 2H), 3.97(s, 3H), 4.07(s, 2H), 6.17(bs, 1H), 6.26(d, 1H), 6.39(dd, 1H) 8.04(d, 1H). Rf 0.85(AcOEt) |
| 37-20 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.08(s, 3H), 3.54(dd, 2H), 3.67(dd, 2H), 3.96(s, 3H), 4.05(s, 2H), 6.25(d, 1H), 6.38(dd, 1H) 8.03(d, 1H). Rf 0.30(AcOEt) |
| 37-21 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.73-1.55(m, 2H), 1.99-1.91(m, 2H), 2.09(s, 3H), 2.61-2.49(m, 5H), 3.47(t, 2H), 3.63(t, 2H), 3.99-3.89(m, 3H), 3.95(s, 3H), 6.32(d, 1H), 6.42(dd, 1H) 8.01(d, 1H). Rf 0.10(AcOEt:MeOH = 4:1) |
| 37-22 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.90(s, 3H), 3.98(s, 3H), 3.98(s, 3H), 6.56(s, 1H), 7.59(s, 1H). Rf 0.605(AcOEt) |

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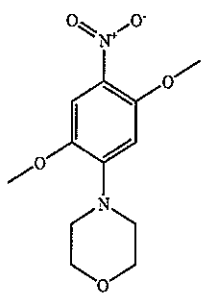
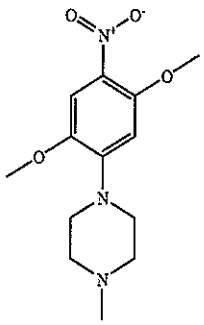
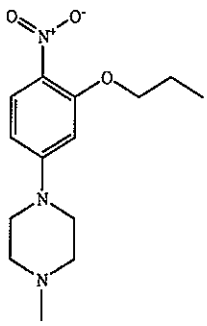
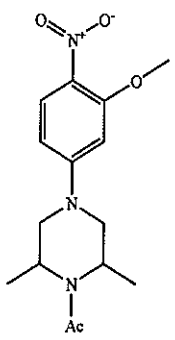
| Ex-No | Rx | Identification |
|---|---|---|
| 37-23 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.25-3.22(m, 4H), 3.90-3.87(m, 4H), 3.95(s, 3H), 6.48(s, 1H), 7.57(s, 1H). Rf 0.060 (Hexane:AcOEt = 5:1) |
| 37-24 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.37(s, 3H), 2.61(bs, 4H), 3.27 (bs, 4H), 3.88(s, 3H), 3.95(s, 3H), 6.48(s, 1H), 7.56(s, 1H). Rf 0.10(AcOEt:MeOH = :1) |
| 37-25 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.09(t, 3H), 1.89(dd, 2H), 2.36(s, 3H), 2.55(t, 4H), 3.39(t, 4H), 4.03(t, 2H), 6.32(d, 1H), 6.42(dd, 1H), 7.98(d, 1H). Rf 0.12(AcOEt:MeOH = 9:1) |
| 37-26 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.36(s, 3H), 1.38(s, 3H), 2.10(s, 2H), 2.17(s, 3H), 3.27-2.96(m, 2H), 3.71(d, 2H), 3.96(s, 3H), 6.33(d, 1H), 6.43(dd, 1H), 8.02(d, 1H). Rf 0.10(AcOEt) |

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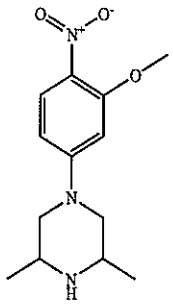
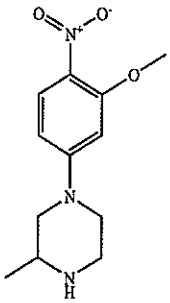
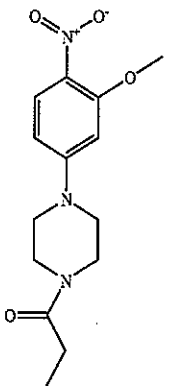
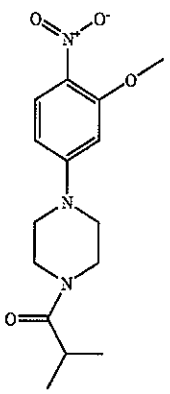
| Ex-No | Rx | Identification |
|---|---|---|
| 37-27 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.16(s, 3H), 1.18(s, 3H), 2.50(dd, 2H), 3.02-2.47(m, 2H), 3.69(dd, 2H), 3.96(s, 3H), 6.31(d, 1H), 6.43(dd, 1H), 8.00(d, 1H). Rf 0.070(AcOEt) |
| 37-28 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.16(d, 3H), 2.57(dd, 1H), 3.00-2.89 (m, 4H), 3.18-3.11(m, 1H), 3.75-3.68(m, 2H), 3.96(s, 3H), 6.31(d, 1H), 6.43(dd, 1H), 8.01(d, 1H). Rf 0.070(AcOEt) |
| 37-29 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.18(t, 3H), 2.40(dd, 2H), 3.47-3.38 (m, 4H), 3.71-3.63(m, 2H), 3.85-3.79(m, 2H), 3.96(s, 3H), 6.32(d, 1H), 6.42(dd, 1H), 8.01(d, 1H). Rf 0.20(AcOEt) |
| 37-30 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.16(s, 3H), 1.18(s, 3H), 2.82(sept, 1H), 3.50-3.37(m, 4H), 3.77-3.65(m, 2H), 3.86-3.78(m, 2H), 3.96(s, 3H), 6.33(d, 1H), 6.43(dd, 1H), 8.01(d, 1H). Rf 0.48 (AcOEt) |

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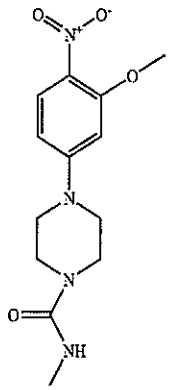
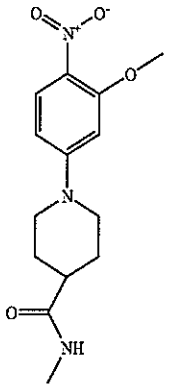
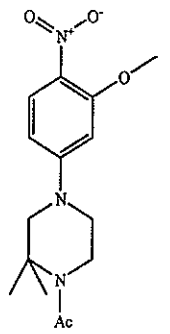
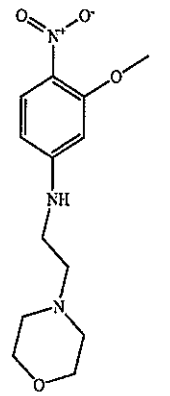
| Ex-No | Rx | Identification |
|---|---|---|
| 37-31 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.86(d, 3H), 3.48-3.45(m, 4H), 3.61-3.58(m, 4H), 3.96(s, 3H), 4.48-4.37(m, 1H), 6.29(d, 1H), 6.40(dd, 1H), 8.01(d, 1H). Rf 0.20(AcOEt) |
| 37-32 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.72-1.60(m, 2H), 2.06-1.97(m, 2H), 3.25-3.17(d, 3H), 3.78-3.70(m, 2H), 3.95(s, 3H), 4.04-3.99 (m, 1H), 6.33(d, 1H), 6.43(dd, 1H), 8.00(d, 1H). Rf 0.20 (AcOEt) |
| 37-33 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.53(s, 6H), 2.14(s, 3H), 3.50(s, 2H), 3.61-3.58(m, 2H), 3.97-3.81(m, 2H), 3.97(s, 3H), 6.10(d, 1H), 6.26(dd, 1H), 8.05(d, 1H). Rf 0.030(AcOEt) |
| 37-34 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.54-2.23(m, 4H), 2.67(t, 2H), 3.29-3.23(m, 2H), 3.74(t, 4H), 3.94(s, 3H), 6.07(d, 1H), 6.16 (dd, 1H), 8.00(d, 1H). Rf 0.15(AcO |

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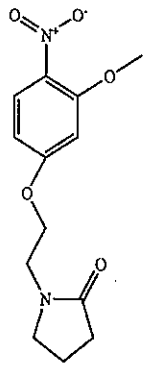
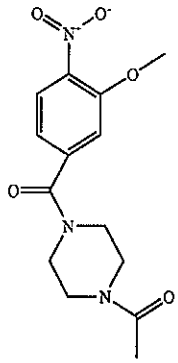
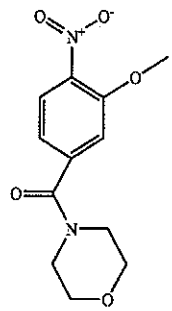
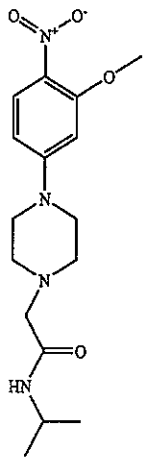
| Ex-No | Rx | Identification |
|---|---|---|
| 37-35 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.10-2.02(m, 2H), 2.41(t, 2H), 3.56(dd, 2H), 3.71(t, 2H), 3.95(s, 3H), 4.19(t, 2H), 6.49(dd, 1H), 6.55(d, 1H), 7.99(d, 1H). Rf 0.10(AcOEt) |
| 37-36 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.14(s, 3H), 3.87-3.34(m, 8H), 3.99 (s, 3H), 7.01(dd, 1H), 7.16(d, 1H), 7.88(d, 1H). Rf 0.25 (AcOEt) |
| 37-37 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.49-3.37(m, 2H), 3.88-3.55(m, 6H), 3.99(s, 3H), 7.00(dd, 1H), 7.16(d, 1H), 7.87(d, 1H). Rf 0.50(AcOEt) |
| 37-38 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.17(s, 3H), 1.19(s, 3H), 2.69(t, 4H), 3.06(s, 2H), 3.42(t, 4H), 3.96(s, 3H), 4.13(sept, 1H), 6.34 (d, 1H), 6.44(dd, 1H), 6.90-6.79(m, 1H), 8.00(d 1H). Rf 0.20 (AcOEt) |

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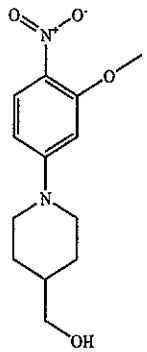
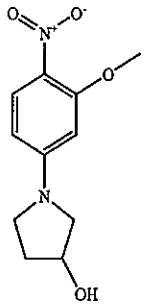
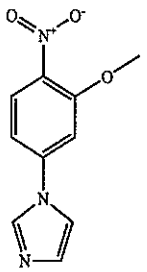
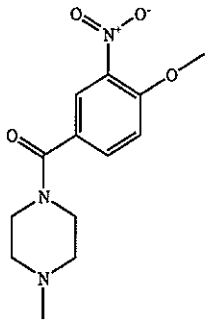
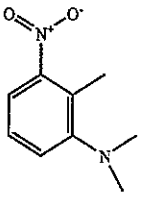
| Ex-No | Rx | Identification |
|---|---|---|
| 37-39 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.44-1.34(m, 2H), 1.84-1.77(m, 1H), 1.94-1.85(m, 2H), 3.04-2.94(m, 2H), 3.55(t, 2H), 3.96-3.57 (m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.00(d, 1H). Rf 0.30(AcOEt) |
| 37-40 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.44-1.34(m, 2H), 1.84-1.77(m, 1H), 1.94-1.85(m, 2H), 3.04-2.94(m, 2H), 3.55(t, 2H), 3.96-3.57 (m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.04(d, 1H). Rf 0.45(AcOEt) |
| 37-41 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 4.05(s, 3H), 7.07(d, 1H), 7.08(d, 1H), 7.27-7.26(m, 1H), 7.33(t, 1H), 7.92(s, 1H), 8.04(d, 1H). Rf: 0.20(AcOEt) |
| 37-42 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.34(s, 3H), 2.55-2.37(m, 4H), 3.86-3.38(m, 4H), 4.00(s, 3H), 7.13(d, 1H). 7.66(dd, 1H). 7.93(d, 1H). Rf: 0.30(AcOEt:MeOH = 4:1) |
| 37-43 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.43(s, 3H), 2.74(s, 6H), 7.91(dd, 1H), 7.23(d, 1H), 7.24(d, 1H), 7.46(dd, 1H). Rf: 0.70(Hexane:AcOEt = 5:1) |

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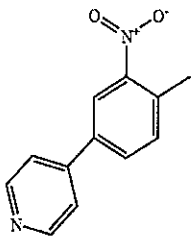
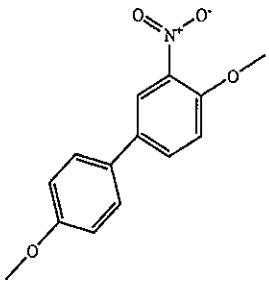
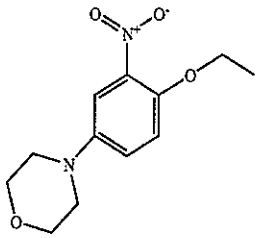
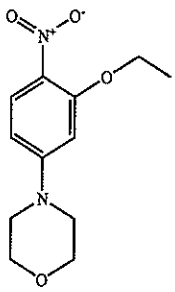
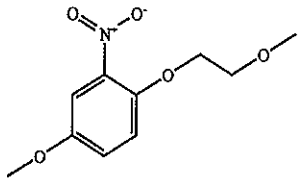
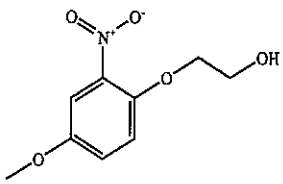
| Ex-No | Rx | Identification |
|---|---|---|
| 37-44 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.15(s, 3H), 3.80-3.48(m, 2H), 6.87(dd, 1H), 6.92(dd, 1H), 7.09(d, 1H), 7.40 (dd, 2H), 8.54(dd, 2H). |
| 37-45 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.86(s, 3H), 4.00(s, 3H), 6.78(d, 1H), 6.99(dd, 2H), 7.14(d, 1H), 7.48(dd, 2H), 7.71(dd, 1H), 8.03(d, 1H). Rf: 0.30 (Hexane:AcOEt = 3:1) |
| 37-46 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.44(t, 3H), 3.10(t, 4H), 3.86(t, 4H), 4.13(q, 2H), 7.01(dd, 1H), 7.08(dd, 1H), 7.35(d, 1H). Rf: 0.25(Hexane:AcOEt = 3:1) |
| 37-47 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.26(t, 3H), 3.32(t, 4H), 3.85(t, 4H), 4.15(q, 2H),6.34(d, 1H), 6.42(dd, 1H), 7.98(d, 1H). Rf: 0.45(Hexane:AcOEt = 5:1) |
| 37-48 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.45(s, 3H), 3.77(dd, 2H), 3.81(s, 3H), 4.06(t, 2H), 7.08---7.08(m, 2H), 7.37(t, 1H). Rf: 0.45(Hexane:AcOEt = 3:1) |
| 37-49 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.44(t, 1H), 3.53(s, 3H), 3.96(ddd, 2H), 4.20(t, 2H), 7.06(d, 1H), 7.12(dd, 1H), 7.40(d, 1H). Rf: 0.10(Hexane:AcOEt = 3:1) |

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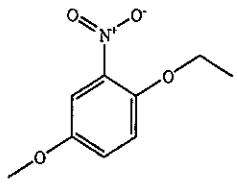
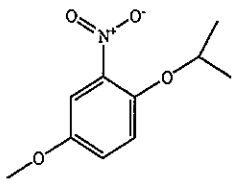
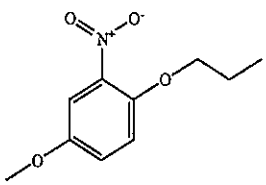
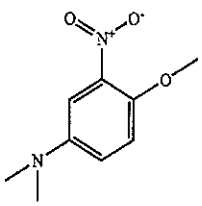
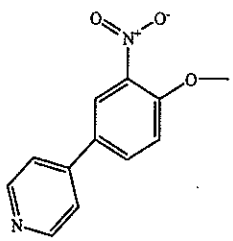
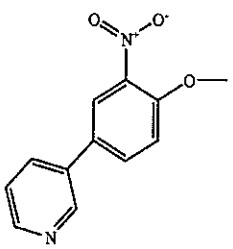
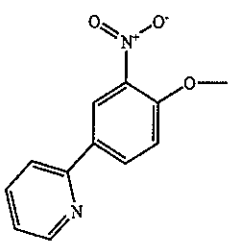
| Ex-No | Rx | Identification |
|---|---|---|
| 37-50 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.45(t, 3H), 3.81(s, 3H), 4.13(q, 2H), 7.01(d, 1H), 7.08(dd, 1H), 7.36(d, 1H). Rf: 0.20(Hexane:AcOEt = 3:1) |
| 37-51 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.35(s, 3H), 1.36(s, 3H), 3.81(s, 3H), 4.52(sept, 1H), 7.08-7.01(m, 2H), 7.31 (d, 1H). Rf: 0.30(Hexane:AcOEt = 3:1) |
| 37-52 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.05(t, 3H), 1.83(ddd, 2H), 3.81(s, 3H), 4.01(t, 2H), 7.01(d, 1H), 7.08(dd, 1H), 7.36(d, 1H). Rf: 0.35(Hexane:AcOEt = 3:1) |
| 37-53 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.86(s, 6H), 3.79(s, 3H), 6.91(dd, 1H), 7.00(d, 1H), 7.18(d, 1H). Rf: 0.5 (Hexane:AcOEt = 9:1) |
| 37-54 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 4.04(s, 3H), 7.22(d, 1H), 7.48(dd, 2H), 7.83(dd, 1H), 8.16(d, 1H), 8.69(dd, 2H). Rf: 0.12(Hexane:AcOEt = 1:1) |
| 37-55 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 4.02(s, 3H), 7.22(d, 1H), 7.39(ddd, 1H), 7.77(dd, 1H), 7.85(ddd, 1H), 8.08(d, 1H), 8.63(dd, 1H), 8.83(d, 1H). Rf: 0.55 (Hexane:AcOEt = 2:1) |
| 37-56 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 4.03(s, 3H), 7.19(d, 1H), 7.28-7.24(m, 1H), 7.72(dd, 1H), 7.80-7.76(m, 1H), 8.25(dd, 1H), 8.52(d, 1H), 8.69(ddd, 1H). Rf: 0.55 (Hexane:AcOEt = 2:1) |

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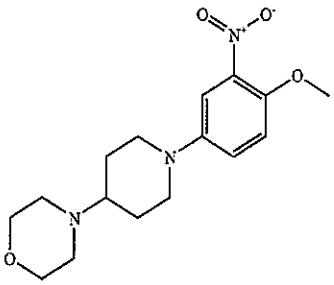
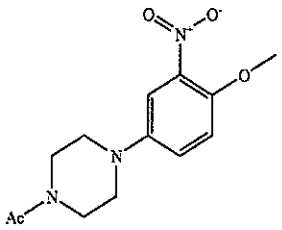
| Ex-No | Rx | Identification |
|---|---|---|
| 37-57 |  | mp 90.7° C.; $^1$H-NMR(400 MHz, $CDCl_3$)δ(ppm): 1.68 (m; 2H), 2.00(m; 2H), 2.36(s; 1H), 2.62(bs; 4H), 2.72(m; 2H), 3.62(m; 2H), 3.78(bs; 4H), 3.90(s; 3H), 6.99(d; 1H); 7.13(dd; 1H), 7.26(s; 1H); 7.40(s; 1H). |

Preparation of 1-[4-(4-Methoxy-3-nitro-phenyl)-piperazin-1-yl]-ethanone

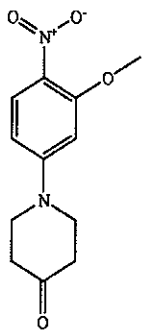


To a solution of 5-bromo-1-methoxy-2-nitrobenzene (300 mg, 1.29 mmol) in dioxane, 1-acetyl piperazine (400 mg, 3.12 mmol), cesium carbonate (1.0 g, 3.07 mmol), palladium diacetate (29.0 mg, 0.129 mmol) and 2-(di-t-butylphosphino)biphenyl (77 mg, 0.258 mmol) are added and stirred at 100° C. for 8 hours. After cooling, the mixture is filtered to remove insoluble material. The filtrate is poured into water and extracted with ethyl acetate twice. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified by silica gel column chromatography (n-hexane:ethyl acetate gradient) to afford 1-[4-(4-Methoxy-3-nitro-phenyl)-piperazin-1-yl]-ethanone (319 mg, 44%) as yellow solids.

$^1$H-NMR (400 MHz, $CDCl_3$, δ, ppm): 2.14 (s, 3H), 3.63 (ddd, 4H), 3.63 (t, 2H), 3.78 (t, 2H), 3.92 (s, 3H), 7.03 (d, 1H), 7.12 (d, 1H), 7.41 (d, 1H). Rf (ethyl acetate): 0.18

39

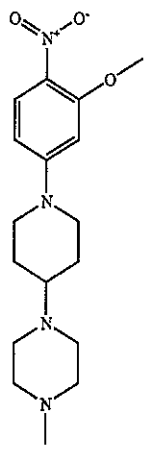
Preparation of 1-(3-Methoxy-4-nitro-phenyl)-piperidin-4-one



To a solution of 4-piperidone hydrochloride monohydrate (10.0 g, 0.065 mol) in DMF (80 mL) are added 4-Fluoro-2-methoxy-1-nitro-benzene (10.0 g, 0.058 mol) and potassium carbonate (20.2 g), and the mixture is stirred at 70° C. for 20 h. After a filtration, the filtrate is poured into $H_2O$ (ca. 300 mL), and the resulting precipitates are collected by a filtration followed by washing with $H_2O$ for several times to give title compound (8.98 g) in 61% yield. Orange solid. $^1$H-NMR (400 MHz, $CDCl_3$, δ): 2.65-2.62 (4H, m), 3.81-3.78 (4H, m), 3.98 (3H, s), 6.34 (1H, d), 6.45 (1H, dd), 8.05 (1H, d).

40

Preparation of 1-[1-(3-Methoxy-4-nitro-phenyl)-piperidin-4-yl]-4-methyl-piperazine

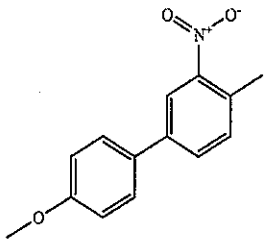


To a solution of 1-(3-Methoxy-4-nitro-phenyl)-piperidin-4-one (4.96 g, 0.020 mol) in dichloroethane (50 ml) is added N-methylpiperazine (2.7 ml, 0.024 mol) at 0° C. and the mixture is stirred at room temperature. After 4 h, sodium triacetoxy-borohydride (5.04 g, 0.024 mol) is added and the mixture is further stirred at room temperature for 24 h. After addition of 1N sodium hydroxide at 0° C., the mixture is poured into water and extracted three times with dichloromethane. The organic layer is combined and extracted three times with 1N hydrochloride. The water layer is basified with 2N sodium hydroxide and extracted three times with dichloromethane. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo to give the title compound as yellow solids (6.04 g) in 91% yield.

$^1$H-NMR (400 MHz, $CDCl_3$, δ): 1.70-1.57 (2H, m), 2.03-1.93 (2H, m), 2.29 (3H, s), 2.55-2.38 (5H, m), 2.70-2.56 (4H, m), 2.97 (2H, ddd), 3.97-3.92 (2H, m), 3.95 (3H, s), 6.31 (1H, d,), 6.42 (1H, dd), 8.00 (1H, d).

41

Preparation of 4'-Methoxy-4-methyl-3-nitro-biphenyl

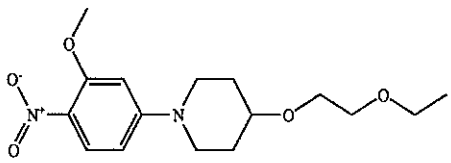


To a solution of 4-methoxyphenyl-boronic acid (500 mg, 3.29 mmol) in toluene (5.2 mL) and ethanol (1.3 mL), potassium carbonate (910 mg, 6.58 mmol), tetrakis(triphenylphosphine)-palladium (228.1 mg, 0.099 mmol) and 4-bromo-1-methyl-2-nitrobenzene (711 mg, 3.29 mmol) are added and stirred at 100° C. for 7 hours. The mixture is poured into water and extracted with ethyl acetate two times. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane:ethyl acetate=5:1) to afford the 4'-methoxy-4-methyl-3-nitro-biphenyl (630 mg, 79%) as a yellow solid.

$^1$H-NMR (400 MHz, $CDCl_3$, δ, ppm): 2.62 (s, 3H), 3.86 (s, 3H), 7.02-6.98 (m,2H), 7.37 (d, 1H), 7.54 (dd, 2H), 7.68 (dd, 1H), 8.18 (d, 1H). Rf (hexane:ethyl acetate=3:1): 0.40.

42

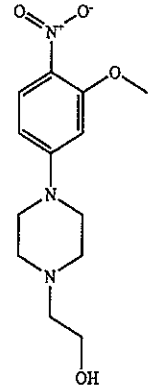
Preparation of 4-(2-Ethoxy-ethoxy)-1-(3-methoxy-4-nitro -phenyl)-piperidine



To a solution of 1-(3-Methoxy-4-nitro-phenyl)-piperidin-4-ol (300 mg, 1.2 mmol) in N,N-dimethylformamide (3.0 mL), sodium hydride (1.52 g, 3.8 mmol) is added. After stirring, 2-bromoethyl methyl ether (150 µl, 1.6 mmol) is added and the mixture is further stirred at 70° C. for 15 hours. After addition of saturated aqueous ammonium chloride, the mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue is purified by silica gel column chromatography (n-hexane-ethyl acetate gradient) to afford 4-(2-Methoxy-ethoxy)-1-(3-methoxy-4-nitro-phenyl)-piperidine (111 mg, 29%) as a yellow oil.

$^1$H-NMR (400 MHz, $CDCl_3$, δ, ppm): 1.52(t, 3H), 1.95-2.00(m, 2H), 1.70-1.79(m, 2H), 3.23(ddd, 2H), 3.58-3.64(m, 2H), 3.65-3.68(m, 2H), 3.64-3.72(m, 2H), 3.95(s, 3H), 6.31 (d, 1H), 6.42(dd, 1H), 8.00(d, 1H). Rf 0.53 (n-hexane: AcOEt=1:1).

According the procedure described above using appropriate alkyl halides, the following compounds are prepared.

| Ex-No. | Rx | Identification |
|---|---|---|
| 42-1 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 2.04-2.21(m, 1H), 2.63(t, 2H), 2.68(t, 2H), 3.42(t, 4H), 3.87(t, 4H), 3.96(s, 3H), 6.33(d, 1H), 6.44(dd, 1H), 8.02(d, 1H). Rf 0.09(AcOEt). |

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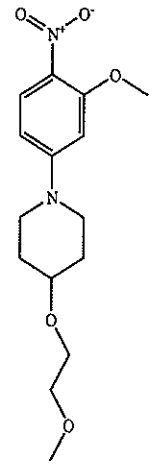
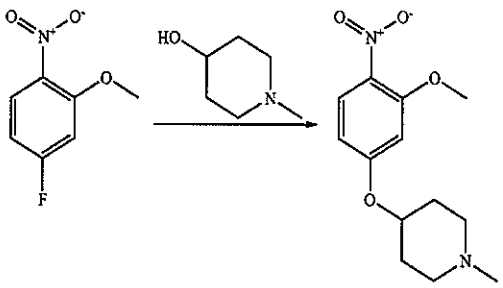
| Ex-No. | Rx | Identification |
|---|---|---|
| 42-2 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.71-1.79(m, 2H), 1.95-2.02 (m, 2H), 3.22(ddd, 2H), 3.40(s, 3H), 3.55-3.57(m, 2H), 3.59-3.73(m, 3H), 3.65-3.67(m, 2H), 3.95(s, 3H), 6.31(d, 1H), 6.42(dd, 1H), 8.00(d, 1H). Rf 0.35(n-hexane:AcOEt = 1:1) |

Example: 43

2-Methoxy-4-(1-methyl-piperidin-4-yloxy)-phenylamine 4-(3-Methoxy-4-nitro-Phenoxy)-1-methyl-piperidine



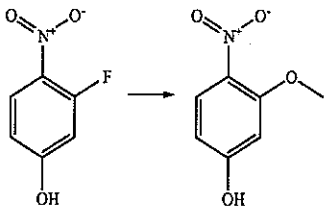
To a solution of 4-Fluoro-2-methoxy-1-nitro-benzene (10.3 g, 60 mmol) in toluene (50 mL) and 25% KOH aq. (50 mL), 4-hydroxy-1-methylpiperidine (13.8 g, 120 mmol) and tetra-n-butyl ammonium bromide (3.87 g, 12 mmol) are added at room temperature. The mixture is heated at 60° C. for 1 day. The reaction mixture is cooled to room temperature, poured into ice water and extracted twice with ethyl acetate. The organic layer is successively washed with dil.HCl and brine, dried over sodium sulfate, and evaporated in vacuo to afford the crude compound in quantitative yield (13.4 g).

Rf=0.22 (methanol:dichloromethane=1:4). $^1$H-NMR (400 MHz, $CDCl_3$, δ, ppm): 1.84-1.92(m, 2H), 2.0-2.1(m, 2H), 2.3-2.4 (m, 2H), 2.33 (s, 3H), 2.65-2.75(m, 2H), 3.94(s, 3H), 4.39-4.46(m, 1H), 6.49 (dd, 1H), 6.99 (d, 1H), 6.54 (d, 1H), 7.99 (d, 1H).

Example: 44

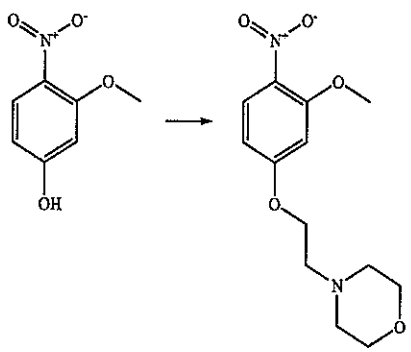
2-Methoxy-4-(2-morpholin-4-yl-ethoxy)-phenylamine

3-Methoxy-4-nitro-phenol



To a solution of 3-Fluoro-4-nitro-phenol (15.7 g, 100 mmol) in THF (300 mL), 30% KOMe in Methanol (49 mL, 210 mmol) is added at 0° C. The mixture is heated to gentle reflux for 18 hours.

4-[2-(3-Methoxy-4-nitro-phenoxy)-ethyl]-morpholine



To a solution of 3-Methoxy-4-nitro-phenol (1.69 g, 10 mmol) in DMF (25 mL), 4-(2-Chloroethyl)morpholine

hydrochloride (2.05 g, 11 mmol), K2CO3 (1.52 g, 11 mmol), KI (332 mg, 2 mmol) are added at room temperature. The mixture is heated to gentle reflux for 4 hours. The reaction mixture is cooled to room temperature and quenched with water. The resulting mixture is extracted twice with ethyl acetate and then the organic layer is successively washed with water and brine, dried over sodium sulfate, filtered and evaporated in vacuo to afford the crude compound in 90% yield (2.55 g).

Rf=0.11 (AcOEt only). $^1$H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.56-2.61(m, 4H), 2.83(t, The reaction mixture is cooled to room temperature and quenched slowly with 1NHCl aq at 0° C. The resulting mixture is extracted twice with ethyl acetate and then the organic layer is successively washed with brine, dried over sodium sulfate, filtered and evaporated in vacuo to afford the crude compound in 94% yield (15.9 g).

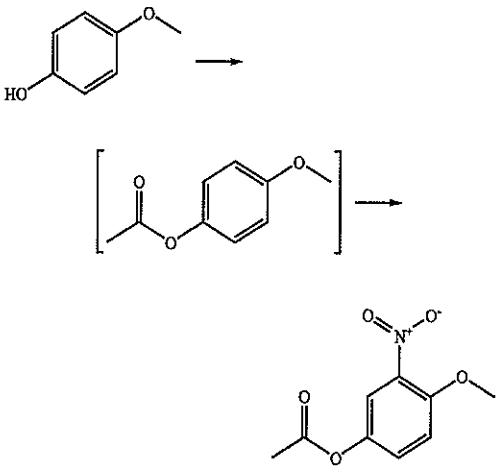
Rf=0.22 (methanol:dichloromethane=1:4). $^1$H-NMR (400 MHz, $CDCl_3$), δ (ppm): 3.95(s, 3H), 5.49(s, 1H), 6.44 (dd, 1H, J=8.8, 2.52 Hz), 6.54 (d, 1H, J=2.52 Hz), 7.96 (d, 1H J=8.6 Hz). 3.72-3.76(m, 4H), 3.94(s, 3H), 4.18(t, 2H), 6.51 (dd, 1H, J=9.08, 2.52 Hz), 6.56 (d, 1H, J=2.48 Hz), 8.00 (d, 1H J=9.08 Hz).

2H),

Example: 45

2-Methoxy(2-morpholin-4-yl-ethoxy)-phenylamine

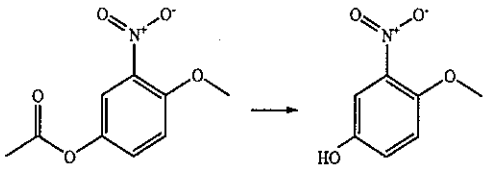
Acetic acid 4-methoxy-3-nitro-phenyl ester



To a solution of 4-Methoxyphenol (12.4 g, 100 mmol) in AcOH (50 mL), $Ac_2O$ (50 mL) is added at room temperature. The mixture is heated to gentle reflux for 1.5 hour. The reaction mixture is cooled to room temperature and c.$HNO_3$ (d=1.38, 10 mL) is added slowly at 0° C. The mixture is heated to 55° C. for 1.5 h. The reaction mixture is cooled to room temperature and quenched with water at 0° C. The resulting solid is filtered on Buchner funnel to afford the crude compound in 76% yield (16.0 g).

Rf=0.59 (AcOEt:n-Hexane=3:7). $^1$H-NMR (400 MHz, $CDCl_3$), δ (ppm): 2.31(s, 3H), 3.96(s, 3H), 7.08 (d, 1H, J=9.04 Hz), 7.31 (dd, 1H, J=9.04, 3.04 Hz), 7.96 (d, 1H J=3.04 Hz).

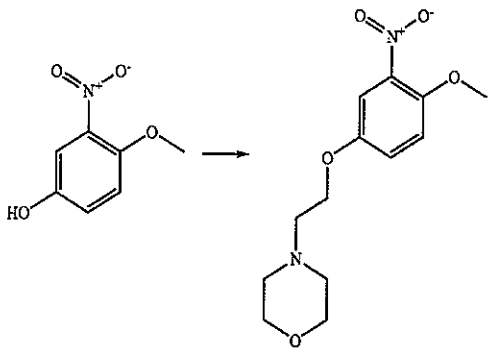
4-Methoxy-3-nitro-phenol



To a solution of Acetic acid 4-methoxy-3-nitro-phenyl ester (1.06 g, 5 mmol) in EtOH (20 mL), 1N NaOH aq (5.5 mL) is added at 0° C. The mixture is stirred at room temperature for 2 hours. The reaction mixture is quenched with AcOH and extracted twice with ethyl acetate. The organic layer is successively washed with water and brine, dried over sodium sulfate, filtered and evaporated in vacuo to afford the crude compound in quantitative yield (840 mg).

Rf=0.59 (AcOEt:n-Hexane=3:7). $^1$H-NMR (400 MHz, $CDCl_3$), δ (ppm): 3.91 (s, 3H), 6.99 (d, 1H, J=9.04 Hz), 7.17 (dd, 1H, J=9.04, 3.00 Hz), 7.38 (d, 1H J=3.04 Hz).

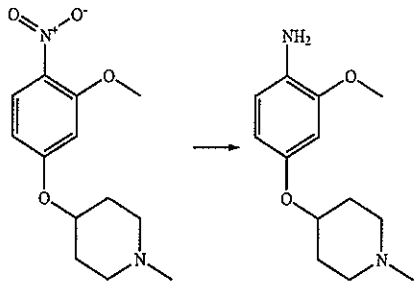
4-[2-(4-Methoxy-3-nitro-phenoxy)-ethyl]-morpholine



To a solution of 4-Methoxy-3-nitro-phenol (1.01 g, 6 mmol) in DMF (15 mL) 4-(2-Chloroethyl)morpholine hydrochloride (1.34 g, 7.2 mmol), K2CO3 (2.49 g, 18 mmol), KI (2.99 g, 18 mmol) are added at room temperature. The mixture is heated to 80° C. for 4 hours. The reaction mixture is cooled to room temperature and quenched with saturated NH4Cl solution in water. The resulting mixture is extracted twice with ethyl acetate and then the organic layer is successively washed with water and brine, dried over sodium sulfate, filtered and evaporated in vacuo to afford the crude compound in quantitative yield (1.70 g). Rf=0.14 (AcOEt only). $^1$H-NMR (400 MHz, DMSO, δ, ppm): 2.36-2.51 (m,

4H), 2.67 (t, J=5.5, 2H), 3.52-3.60 (m, 4H), 3.86 (s, 3H), 4.11 (t, J=6.0, 2H), 7.25-7.29 (m, 2H), 7.46-7.49 (m, 1H).

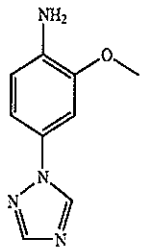
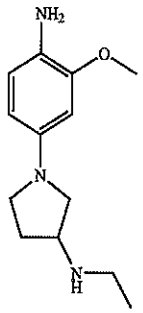
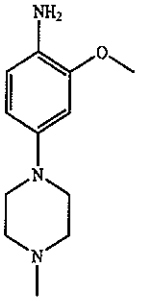
Preparation of 2-Methoxy-4-(1-methyl-piperidin-4-yloxy)-phenylamine



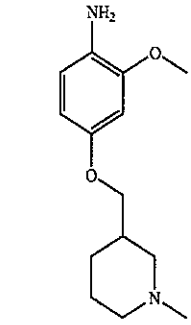
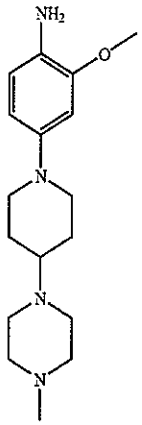
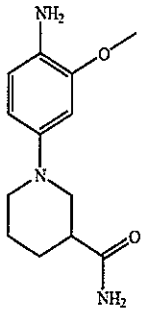
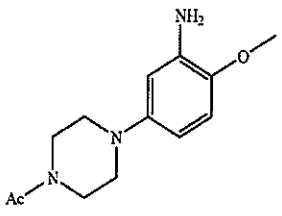
To a solution of 4-(3-Methoxy-4-nitro-phenoxy)-1-methyl-piperidine (3.0 g, 11.3 mmol) in ethanol (50 mL), 5% palladium on carbon (300 mg) is added under a nitrogen atmosphere. The reaction vessel is fitted with a balloon adapter and charged with hydrogen and evacuated three times until the reaction is under a hydrogen atmosphere. The reaction is allowed to stir overnight. The reaction mixture is filtered through a pad of Celite and washed with methanol. The filtrate is concentrated in vacuo to afford 2-Methoxy-4-(1-methyl -piperidin-4-yloxy)-phenylamine in quantitative yield (2.7 g).

Rf=0.41 (methanol:dichloromethane=1:1). $^1$H-NMR (400 MHz, $CDCl_3$), δ (ppm): 1.75-1.86(m, 2H), 1.92-2.05(m, 2H), 2.2-2.32 (m, 2H), 2.30 (s, 3H), 3.4-3.7(brs, 2H), 3.82(s, 3H), 4.14.2(m, 1H), 6.37(dd, 1H), 6.46 (d, 1H), 6.61 (d, 1H).

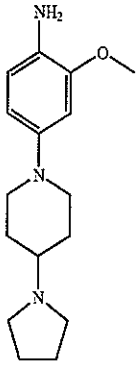
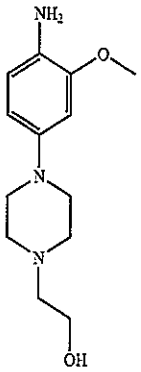
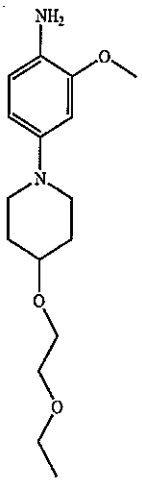
By repeating the procedures described above using appropriate starting materials and conditions the following compounds are obtained.

| Ex-No. | Rx | Identification |
|---|---|---|
| 46-1 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 3.92(s, 3H), 3.97(br,H), 6.75(d, 1H), 7.00(dd, 1H), 7.12(d, 1H), 8.06(s, 1H), 8.41(s, 1H). Rf 0.32(AcOEt) |
| 46-2 |  [1-(4-Amino-3-methoxy-phenyl)-pyrrolidin-3-yl]-ethyl-amine | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.13(t, 3H), 1.77-1.86(m, 1H), 2.19-2.27(m, 1H), 2.67-2.75(m, 2H), 3.01-3.06(m, 1H), 3.20-3.26(m, 1H), 3.33-3.38(m, 1H), 3.42-3.49(m, 2H), 3.84(s, 3H), 6.04-6.07(m, 1H), 6.14-6.15(m, 1H), 6.64-6.66(m, 1H). Rf 0.2(AcOEt only) |
| 46-3 |  2-Methoxy-4-(4-methyl-piperazin-1-yl)-phenylamine | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 2.44(s, 3H), 2.70-2.73(m, 4H), 3.13-3.17(m, 4H), 3.48(brs, 2H), 3.84(s, 3H), 6.41(dd, 1H, J=8.5, 2.52 Hz), 6.51(d, 1H, J=2.52 Hz), 6.64(d, 1H, J=8.5 Hz). Rf 0.2(AcOEt only). |

-continued

| Ex-No. | Rx | Identification |
|---|---|---|
| 46-4 |  2-Methoxy-4-(1-methyl-piperidin-3-ylmethoxy)-phenylamine | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.01-1.12(m, 1H), 1.57-2.13 (m, 6H), 2.26(s, 3H), 2.74-2.77(m, 1H), 2.93-2.96(m, 1H), 3.47(bs, 2H), 3.70-3.80(m, 2H), 3.82(s, 3H), 6.31-6.34(m, 1H), 6.44-6.45(m, 1H), 6.60-6.62(m, 1H). Rf 0.2(AcOEt only) |
| 46-5 |  | $^1$H-NMR(400 MHz, $CDCl_3$) 1.80-1.67(2H, m), 1.99-1.90 (2H, m), 2.42-2.27(1H, m), 2.56-2.43(4H, m), 2.68-2.58(2H, m), 2.76-2.58(4H, m), 3.57-3.48(2H, m), 3.83(3H. s), 6.41 (1H, dd), 6.52(1H, d), 6.63(1H, d). $R_f$(hexane/acetone 1:1) 0.44. |
| 46-6 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.83-1.95(m, 2H), 1.97-2.08 (m, 2H), 2.20-2.31(m, 1H), 2.60-2.72(m, 2H), 3.46-3.53 (m, 2H), 3.84(s, 3H), 5.42-5.60(m, 1H), 6.43(dd, 1H), 6.53 (d, 1H), 6.64(d, 1H). |
| 46-7 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 2.13(s, 3H), 3.01-3.05 (m, 4H), 3.59(t, 2H), 3.75(t, 2H), 3.81(s, 3H), 6.30(dd, 1H), 6.39(bs, 1H), 6.71(d, 1H). |

-continued

| Ex-No. | Rx | Identification |
|---|---|---|
| 46-8 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.84-1.97(m, 2H), 1.98-2.07 (m, 2H), 2.20-2.32(m, 1H), 2.61-2.72(m, 2H), 3.47-3.55 (m, 2H), 3.95(s, 3H), 5.20-5.38(m, 1H), 5.40-5.56(m, 2H), 6.43(d, 1H), 6.53(bs, 1H), 6.64(d, 1H). |
| 46-9 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 2.59-2.67(m, 2H), 2.77-2.68 (m, 4H), 3.08-3.15(m, 4H), 3.49-3.56(m, 1H), 3.67-3.77 (m, 2H), 3.98(s, 3H), 6.41-6.43(m, 1H), 6.52(bs, 1H), 6.65 (d,1H). |
| 46-10 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.72-1.96(m, 2H), 1.98-2.10 (m, 2H), 2.63(s, 3H), 2.73-2.84(m, 2H), 3.40(s, 3H), 3.34-3.42(m, 2H), 3.44-3.49(m, 1H), 3.55-3.57(m, 2H), 3.64-3.66 (m, 2H), 3.83(s, 3H), 6.41-6.43(m, 1H), 6.53(bs, 1H), 6.63(d, 1H). |

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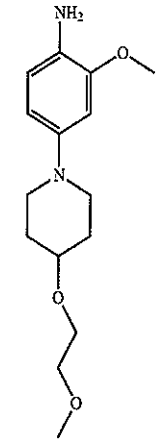
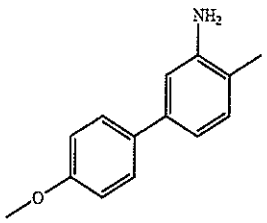
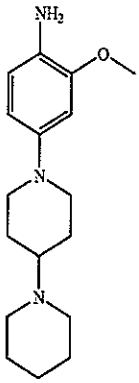
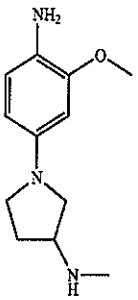
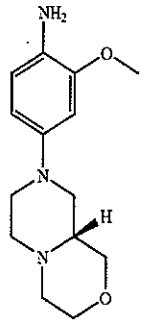
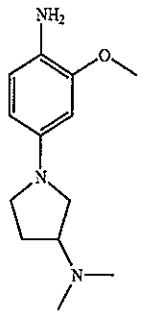
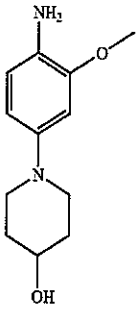
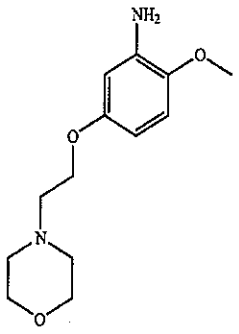
| Ex-No. | Rx | Identification |
|---|---|---|
| 46-11 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.22(t, 3H), 1.72-1.84(m, 2H), 2.00-2.10(m, 2H), 2.72-2.82(m, 2H), 3.33-3.38(m, 2H), 3.43-3.49(m, 1H), 3.55(q, 2H), 3.58-3.61(m, 2H), 3.64-3.66 (m, 2H), 3.83(s, 3H), 6.41-6.43(m, 1H), 6.53(bs, 1H), 6.63 (d, 1H). |
| 46-12 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 2.20(s, 3H), 3.84(s, 3H), 6.87(d, 1H), 6.89(dd, 1H), 6.95(d, 2H), 7.09(d, 1H), 7.48(d, 2H). Rf (n-hexane:ethyl acetate = 1:1):0.50. |
| 46-13 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.49-1.59(m, 3H), 1.70-1.95 (m, 6H), 2.00-2.20(m, 2H), 2.60-2.90(m, 7H), 3.50-3.60 (m, 3H), 3.83(s, 3H), 3.85-3.91(m, 1H), 6.41(dd, 1H, J=8.0, 2.5 Hz), 6.50(d, 1H, J=2.5 Hz), 6.63(d, 1H, J=8.0 Hz) |
| 46-14 |  | $^1$H-NMR(400 MHz, DMSO-d6, δ, ppm): 1.87-1.79(m, 1H), 2.22(ddd, 1H), 2.48(s, 3H), 3.05(dd, 1H), 3.28-3.21(m, 1H), 3.40-3.32(m, 2H), 3.45(dd, 1H), 3.84(s, 3H), 6.06(dd, 1H), 6.15(d, 1H)), 6.66(d, 1H) |

-continued

| Ex-No. | Rx | Identification |
|---|---|---|
| 46-15 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 2.35-2.73(m, 4H), 2.68-2.75 (m, 1H), 2.82-2.93(m, 2H), 3.14-3.19(m, 1H), 3.29-3.40 (m, 2H), 3.50-3.60(bs, 2H), 3.69-3.78(m, 2H), 3.84(s, 3H), 3.85-3.91(m, 1H), 6.40(dd, 1H, J=8.0, 2.5 Hz), 6.50 (d, 1H, J=2.5 Hz), 6.64(d, 1H, J=8.0 Hz) |
| 46-16 |  | $^1$H-NMR(400 MHz, DMSO-d6, δ, ppm): 1.95-1.85(m, 1H), 2.22-2.14(m, 1H), 2.31(s, 3H), 2.89-2.79(m, 1H), 3.10(t, 1H), 3.39-3.25(m, 3H), 3.42(t, 1H), 3.85(s, 3H), 6.05(dd, 1H), 6.14(d, 1H), 6.67(d, H) |
| 46-17 |  | $^1$H-NMR(400 MHz, $CDCl_3$, δ, ppm): 1.68-1.81(m, 2H), 1.97-2.09 (m, 2H), 2.74-2.87(m, 2H), 3.31-3.41(m, 2H), 3.77-3.88 (m, 1H), 3.84(s, 3H), 6.40-6.48(m, 1H), 6.65(bs, 1H), 6.64 (d, 1H). |
| 46-18 |  | $^1$H-NMR(400 MHz, $CDCl_3$), δ(ppm): 2.55-2.61(m, 4H), 2.80(t, 2H), 3.72-3.77(m, 4H), 3.81(s, 3H), 4.05(t, 2H), 6.24(dd, 1H, J=8.56, 2.52 Hz), 6.34(d, 1H, J=2.52 Hz), 6.68(d, 1H J=8.56 Hz). Rf = 0.31(methanol:dichloromethane = 1:9). |

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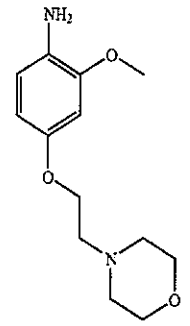
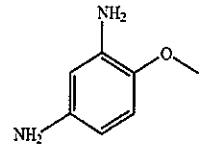
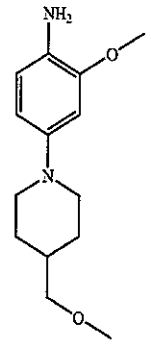
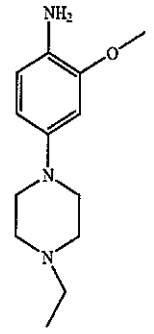
| Ex-No. | Rx | Identification |
|---|---|---|
| 46-19 |  | $^1$H-NMR(400 MHz, $CDCl_3$), δ(ppm): 2.55-2.61(m, 4H), 2.78(t, 2H), 3.72-3.77(m, 4H), 3.82(s, 3H), 4.05(t, 2H), 6.35(dd, 1H, J=8.56, 2.52 Hz), 6.47(d, 1H, J=2.52 Hz), 6.63(d, 1H J=8.56 Hz). Rf = 0.61(methanol:dichloromethane = 1:4). |
| 46-20 |  | $^1$H-NMR(DMSO), δ(ppm): 3.84(s, 3H), 6.95-7.00(m, 1H), 7.08-7.12(m, 2H). |
| 46-21 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.47-1.34(m, 2H), 1.75-1.63(m, 1H), 1.86-1.79(m, 2H), 2.64-2.58(m, 2H), 3.28(d, 2H), 3.61(d, 3H), 3.87(s, 3H), 3.36(s, 1H), 3.49-3.45(m, 2H), 3.84(s, 3H), 6.43(dd, 1H), 6.53(d, 1H) 6.64(d, 1H) |
| 46-22 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.13(t, 3H), 2.49(dd, 2H), 2.68-2.59 (m, 4H), 3.10(t, 4H), 3.84(s, 3H), 6.43(dd, 1H), 6.53(d, 1H) 6.65(d, 1H) |

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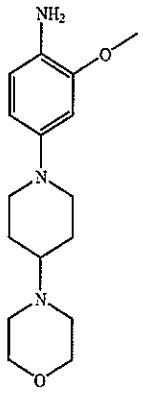
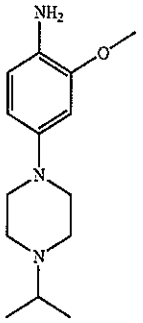
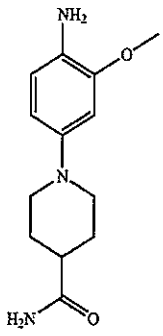
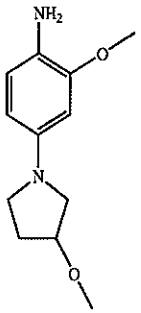
| Ex-No. | Rx | Identification |
|---|---|---|
| 46-23 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.78-1.68(m, 2H), 1.99-1.89(m, 2H), 2.36-2.20(m, 1H), 2.67-2.50(m, 6H), 3.56-3.48(m, 2H), 3.79-3.69(m, 4H), 3.84(s, 3H), 6.42(dd, 1H), 6.52(d, 1H) 6.64(d, 1H) |
| 46-24 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.08(s, 3H), 1.10(s, 3H), 2.69(t, 4H), 2.72-2.68(m, 1H), 3.08(t, 4H), 3.83(s, 3H), 6.42(dd, 1H), 6.53(d, 1H) 6.64(d, 1H) |
| 46-25 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.96-1.84(m, 2H), 2.07-1.99(m, 2H), 2.32-2.28(m, 1H), 2.70-2.60(m, 2H), 3.54-3.47(m, 2H), 3.84(s, 3H), 5.35-5.24(m, 1H), 5.50-5.45(m, 1H), 6.42(dd, 1H), 6.52(d, 1H) 6.64(d, 1H) |
| 46-26 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.18-2.03(m, 2H), 3.28-3.19(m, 2H), 3.39-3.31(m, 1H), 3.36(s, 3H), 3.49-3.42(m, 1H), 3.85 (s, 3H), 6.07(dd, 1H), 6.16(d, 1H), 6.66(d, 1H) |

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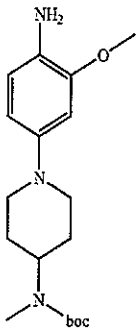
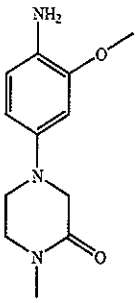
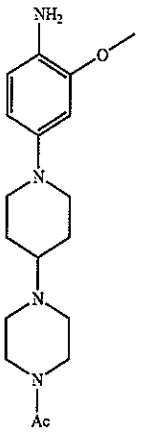
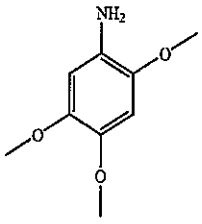
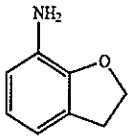
| Ex-No. | Rx | Identification |
|---|---|---|
| 46-27 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.48(s, 9H), 1.88-1.71(m, 2H), 1.97-1.82(m, 2H), 2.78(s, 3H), 2.84-2.64(m, 2H), 3.55-3.48 (m, 2H), 3.95(s, 3H), 3.84(s, 3H), 6.43(d, 1H), 6.52(bs, 1H), 6.64(d, 1H) |
| 46-28 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.02(s, 3H), 3.33(dd, 2H), 3.44(t, 2H), 3.74(s, 2H), 3.83(s, 3H), 6.38(dd, 1H), 6.47(d 1H), 6.66(d, 1H) |
| 46-29 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.78-1.38(m, 2H), 1.98-1.89(m, 2H), 2.30(s, 3H), 2.39-2.31(m, 1H), 2.55-2.42(m, 4H), 2.71-2.56 (m, 6H), 3.35-3.49(m, 2H), 3.83(s, 3H), 6.41(dd, 1H), 6.52(d, 1H) 6.63(d, 1H) |
| 46-30 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.80(s, 3H), 3.82(s, 3H), 3.82(s, 3H), 6.40(s, 1H), 6.54(s, 1H) |
| 46-31 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.20(t, 2H), 4.57(t, 2H), 6.55(dd, 1H), 6.70-6.65(m, 1H), 6.68(d, 1H). Rf 040(AcOEt) |

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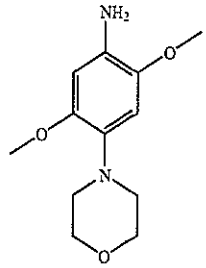
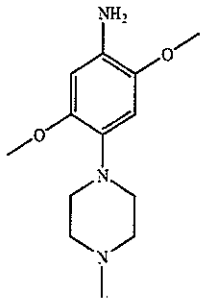
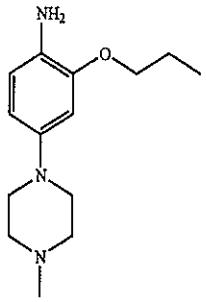
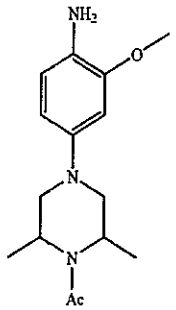
| Ex-No. | Rx | Identification |
|---|---|---|
| 46-32 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.98(t, 4H), 3.62(bs, 2H), 3.79(s, 3H), 3.81(s, 3H), 3.87(t, 4H), 6.36(s, 1H), 6.53(s, 1H) |
| 46-33 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.37(s, 3H), 2.61(t, 4H), 3.27(t, 4H), 3.88(s, 3H), 3.95(s, 3H), 6.48(s, 1H), 7.56(s, 1H) |
| 46-34 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.05(t, 3H), 1.83(ddd, 2H), 2.35(s, 3H), 2.58(t, 4H), 3.07(t, 4H), 3.94(t, 2H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H) |
| 46-35 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.28(s, 3H), 1.30(s, 3H), 2.04(s, 2H), 2.17(s, 3H), 2.84-2.72(m, 2H), 3.20(d, 2H), 3.86(s, 3H), 6.41(d, 1H), 6.46(dd, 1H), 6.66(d, 1H). |

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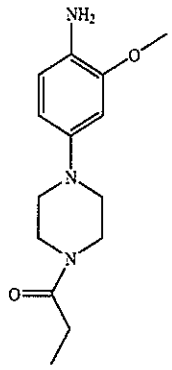
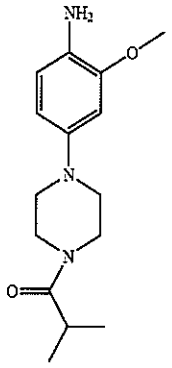
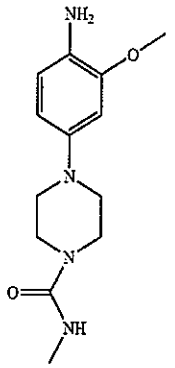
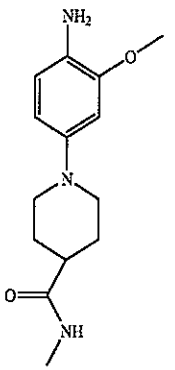
| Ex-No. | Rx | Identification |
|---|---|---|
| 46-36 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.18(t, 3H), 2.39(dd, 2H), 3.07-2.98 (m, 4H), 3.61(t, 2H), 3.78(t, 2H), 3.88(s, 3H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H) |
| 46-37 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.15(s, 3H), 1.16(s, 3H), 2.83(sept, 1H), 3.07-2.98(m, 4H), 3.73-3.64(m, 2H), 3.83-3.76(m, 2H), 3.84(s, 3H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H) |
| 46-38 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.84(d, 3H), 3.02(t, 4H), 3.51(t, 4H), 3.84(s, 3H), 4.48-4.38(m, 1H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H) |
| 46-39 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.99-1.81(m, 2H), 2.23-2.12(m, 2H), 2.69-2.58(m, 2H), 2.84(d, 3H), 3.54-3.45(m, 2H), 3.84(s, 3H), 5.55-5.45(m, 1H), 6.42(dd, 1H), 6.52(d, 1H), 6.64(d, 1H) |

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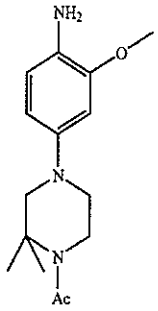
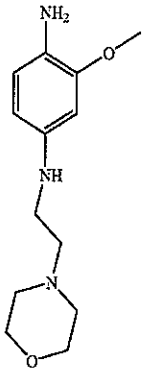
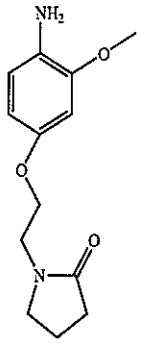
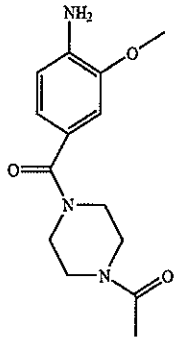
| Ex-No. | Rx | Identification |
|---|---|---|
| 46-40 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.53(s, 6H), 2.11(s, 3H), 3.05(s, 2H), 3.28(t, 2H), 3.64(t, 2H), 3.86(s, 3H), 6.26(dd, 1H), 6.33(d, 1H), 6.67(d, 1H) |
| 46-41 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.55-2.41(m, 4H), 2.63(t, 2H), 3.13(t, 2H), 3.77-3.68(m, 4H), 3.83(s, 3H), 6.15(dd, 1H), 6.25 (d, 1H), 6.62(d, 1H) |
| 46-42 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.05-2.00(m, 2H), 2.39(t, 2H), 3.57(t, 2H), 3.64(t, 2H), 3.83(s, 3H), 4.04(t, 2H), 6.32(dd, 1H), 6.44(d, 1H), 6.63(d, 1H) |
| 46-43 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.13(s, 3H), 3.53-3.46(m, 2H), 3.65-3.55(m, 4H), 3.71-3.66(m, 2H), 3.88(s, 3H), 6.67(d, 1H), 6.87(dd, 1H), 6.95(d, 1H) |

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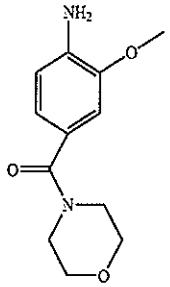
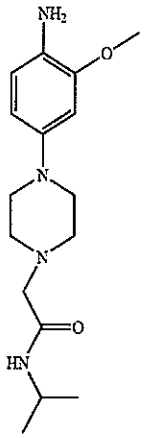
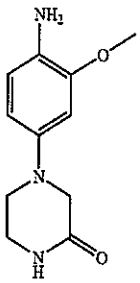
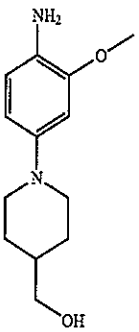
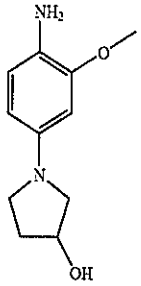
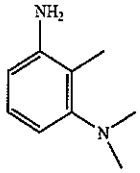
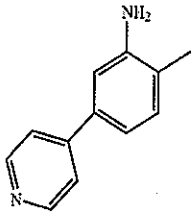
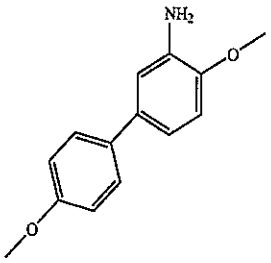
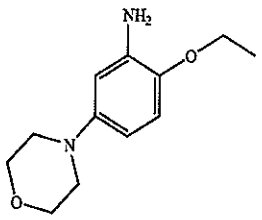
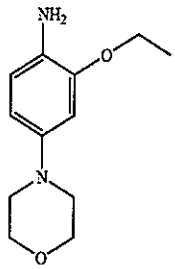
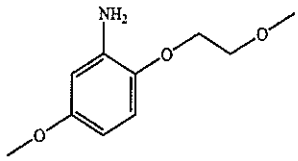
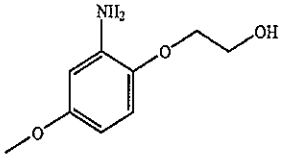
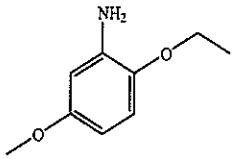
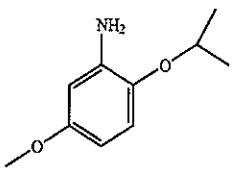
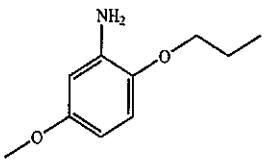
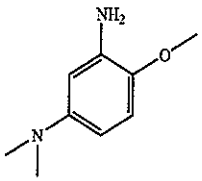
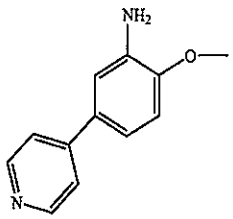
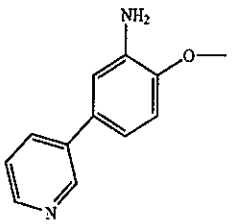
| Ex-No. | Rx | Identification |
|---|---|---|
| 46-44 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.73-3.61(m, 8H), 3.87(s, 3H), 6.65(d, 1H), 6.86(dd, 1H), 6.95(d, 1H) |
| 46-46 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.17(s, 3H), 1.19(s, 3H), 2.69(t, 4H), 3.04(s, 2H), 3.08(t, 4H), 4.15-4.07(m, 1H), 6.41(dd, 1H), 6.51(d, 1H), 6.65(d, 1H), 7.01-6.94(m 1H) |
| 46-47 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.35-3.28(m, 2H), 3.53-3.46(m, 2H), 3.76(s, 2H), 3.84(s, 3H), 5.92-5.83(m, 1H), 6.40(dd, 1H), 6.48(d, 1H), 6.67(d, 1H) |
| 46-48 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.09-2.00(m, 2H), 2.25-2.15(m, 2H), 3.29-3.20(m, 2H), 3.51-3.40(m, 4H), 3.85(s, 3H), 4.62-4.55 (m, 1H), 6.08(d, 1H), 6.18(d, 1H), 6.67(d, 1H) |

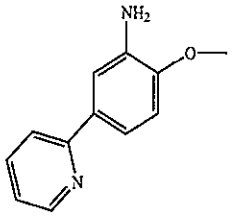
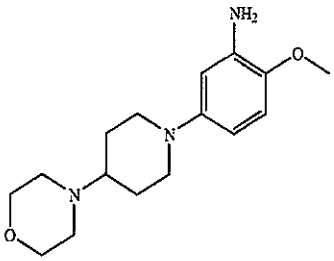
-continued

| Ex-No. | Rx | Identification |
|---|---|---|
| 46-49 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.52-1.40(m, 2H), 1.90-1.84(m, 2H), 2.68-2.59(m, 2H), 3.51-3.45(m, 2H), 3.84(s, 3H), 6.44(dd, 1H), 6.54(d, 1H), 6.64(d, 1H) |
| 46-50 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.14(s, 3H), 2.66(s, 6H), 6.44(d, 1H), 6.54(d, 1H), 6.98(t, 1H). |
| 46-51 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.63(s, 3H), 7.49-7.45(m, 1H), 7.74-7.62(m, 2H), 7.76(dd, 1H), 8.24(d, 1H), 8.77-8.64(m, 2H). |
| 46-52 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.84(s, 3H), 3.88(s, 3H), 6.78(d, 1H), 6.83(d, 1H), 7.00-6.89(m, 3H), 7.45(d, 1H). |
| 46-53 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.40(t, 3H), 3.03(t, 4H), 3.84(t, 4H), 4.00(q, 2H), 6.27(dd, 1H), 6.38(d, 1H), 6.71(dd, 1H), |
| 46-54 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.26(t, 3H), 3.02(t, 4H), 3.85(t, 4H), 4.05(q, 2H), 6.40(dd, 1H), 6.49(d, 1H), 6.66(d, 1H), |

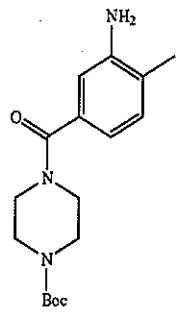
-continued

| Ex-No. | Rx | Identification |
|---|---|---|
| 46-55 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.44(s, 3H), 3.73(s, 3H), 3.74-3.68 (m, 2H), 3.95-3.85(m, 2H), 4.10-4.05(m, 2H), 6.21(dd, 1H), 6.32(d, 1H), 6.75(d, 1H). |
| 46-56 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.35-2.26(m, 1H), 3.74(s, 3H), 3.93-3.86(m, 2H), 4.09-4.07(m, 2H), 6.25(dd, 1H), 6.34(d, 1H), 6.76(d, 1H). |
| 46-57 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.40(t, 3H), 3.71(s, 3H), 4.00(q, 2H), 6.22(dd, 1H), 6.33(d, 1H), 6.69(d, 1H). |
| 46-58 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.32(d, 6H), 3.73(s, 3H), 3.85-3.71 (m, 2H), 4.37(sept, 1H), 6.22(dd, 1H), 6.32(d, 1H), 6.72(d, 1H). |
| 46-59 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 1.04(t, 3H), 1.80(ddd, 2H), 3.72 (s, 3H), 3.85-3.75(m, 2H), 3.90(t, 2H), 6.22(dd, 1H), 6.33(d, 1H), 6.69(d, 1H). |
| 46-60 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 2.94(s, 6H), 3.89(s, 3H), 6.16(dd, 1H), 6.25(d, 1H), 6.72(d, 1H). |
| 46-61 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.91(s, 3H), 6.87(d, 1H), 7.02(dd, 1H), 7.05(d, 1H), 7.44(dd, 2H), 8.59(dd, 2H). |
| 46-62 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.91(s, 3H), 6.88(d, 1H), 6.96-6.93 (m, 1H), 7.31(ddd, 1H), 7.83-7.80(m, 1H), 8.51(dd, 1H), 8.78(dd, 1H). |

-continued

| Ex-No. | Rx | Identification |
|---|---|---|
| 46-63 |  | $^1$H-NMR(400 MHz, $CDCl_3$): 3.91(s, 3H), 6.87(dd, 1H), 7.16(ddd, 1H), 7.34(dd, 1H), 7.43(d, 1H), 7.72-7.64(m, 2H), 8.63-8.61(m, 1H). |
| 46-64 |  | mp 148.6° C.; $^1$H-NMR(500 MHz, $CDCl_3$)δ(ppm): 1.63(m; 2H), 1.99(m; 2H), 2.27(m; 1H), 2.60(m; 6H), 3.52(m; 2H), 3.71 (m; 4H), 3.78(s; 3H), 6.36(dd; 1H); 6.52(d; 1H), 6.73(d; 1H). |

Preparation of 4-(3-amino-4-methylbenzoyl)-piperazine-1-carboxylic acid tert-butyl ester

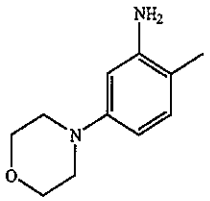


To a solution of 4-methyl-3-nitro-benzoic acid (300 mg, 2.76 mmol), N -butoxycarbonyl-piperazine (340 mg, 1.83 mmol) in DMF (3.0 mL), triethylamine (300 μL, 3.59 mmol), TBTU (800 mg, 2.49 mmol) and HOAt (270.5 mg, 1.99 mmol) are added and stirred at room temperature for 24 hours. The mixture is poured into water and extracted twice with ethyl acetate. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n -hexane:ethyl acetate=5:1) to afford 4-(4-methyl-3-nitrobenzoyl)-piperazine-1-carboxylic acid tert-butyl ester as a colorless solid.

$^1$H-NMR (δ, ppm): 1.47 (s,9H), 2.64 (s, 3H), 3.88-3.28 (m, 8H), 7.42 (d, 1H), 7.56 (dd, 1H), 8.03 (d, 1H). Rf (hexane: ethyl acetate=10:1): 0.13.

The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Preparation of 4-(3-amino-4-methylphenyl)-morpholine

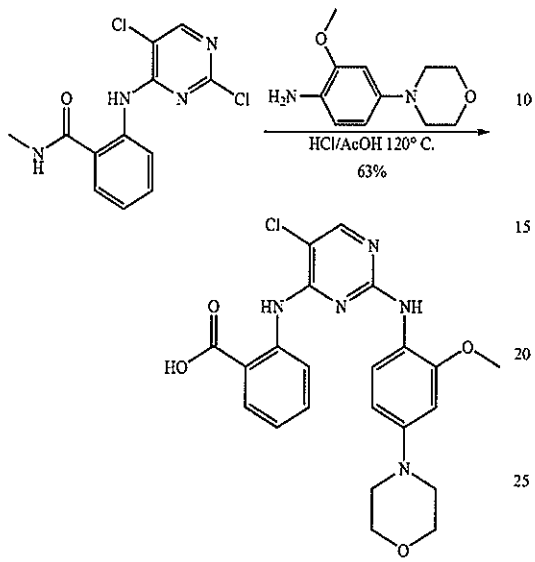


To a suspension of 4-bromo-1-methyl-2-nitrobenzene (225 mg, 1.04 mmol), morpholine (125 μL, 1.25 mmol), and cesium carbonate (474.4 mg, 1.46 mmol) in toluene, palladium diacetate (31.2 mg, 0.139 mmol) and 2-(di-t-butylphosphino)biphenyl (125 mg, 0.403 mmol) are added and stirred at 100° C. for 5 hours. After cooling, the mixture is filtered to remove insoluble material. The filtrate is poured into water and extracted with ethyl acetate twice. The organic layer is washed with water and then brine, dried over magnesium sulfate, and evaporated in vacuo. The residue is purified with silica gel column chromatography (n-hexane:ethyl acetate=5:1) to afford 4-(4-methyl-3-nitrophenyl)-morpholine as a yellow solid.

$^1$H-NMR (δ, ppm): 2.50 (s, 3H), 3.19-3.17 (m, 4H), 3.88-3.86 (m, 4H), 7.04 (dd, 1H), 7.21 (d, 1H), 7.47 (d, 1H). Rf (hexane:ethyl acetate=5:1): 0.20.

The title compound is obtained by reduction with hydrogen over 10% palladium on charcoal in methanol solution.

Preparation of 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-benzoic acid




To a solution of 1.0 g (3.37 mmol) of 2-(2,5-dichloropyrimidin-4-ylamino)-N-methyl-benzamide in 15 mL of acetic acid are added 2-methoxy-4-morpholinoaniline dihydrochloride (1.9 g, 6.73 mmol) and 6.0 mL of 1N ethanolic solution of hydrogen chloride (6.0 mmol). After the reaction mixture is stirred at 120° C. for 16 hours and cooled to mom temperature, aqueous $NaHCO_3$ solution is added to adjust the acidity between pH 5 and pH 6. The resulting precipitate is collected by a filtration and dried under reduced pressure to give 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-benzoic acid (970 mg, 2.12 mmol, 63%) as ivory solid.

NMR (400 MHz, DMSO-d6, δ): 3.10-3.20 (m, 4H), 3.78 (s, 3H), 3.70-3.80 (m, 4H), 6.52 (dd, 1H, J=8.56, 2.52 Hz), 6.67 (d, 1H, J=2.52 Hz), 7.08 (dd, 1H, J=8.04, 8.04 Hz), 7.39 (d, 1H, J=8.56 Hz), 7.35-7.45 (m, 1H), 7.99 (dd, 1H, J=8.04, 1.52 Hz), 8.14 (s, 1H), 8.28 (s, 1H) 8.70-8.80 (m, 1H).

Example 50

Sulfonamide Moieties are Prepared as Follows

Preparation of 2-amino-4-chloro-5-methyl-benzenesulfonyl chloride

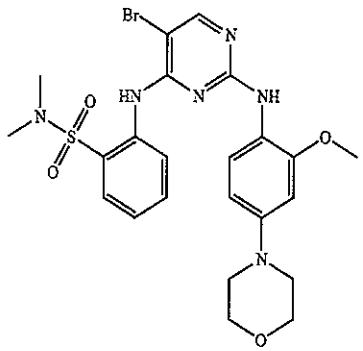
To a solution of 2-amino-5-chloro-4-methyl-benzenesulfonic acid (3.0 g, 1.35 mmol) in dichloroethane (10 mL) is added sulfuryl chloride (4.4 mL, 3.83 mmol) and stirred at 60° C. After one hour, thionyl chloride (1.3 mL) is added and the mixture is further stirred at 100° C. for 7.0 hours. The mixture is poured into iced water and extracted with ether three times. The organic layer is washed with water and then brine, dried over sodium sulfate, and evaporated in vacuo.

$^1$H-NMR (δ, ppm): 2.35 (s, 3H), 6.68 (s, 1H), 7.75 (s, 1H).

This substituted sulfonyl chloride is reacted with a suitable amine. On reaction e.g. with methylamine, 2-amino-5-chloro-4,N-dimethylbenzenesulfonamide is formed.

Example 51

Preparation of 2-[5-bromo-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N,N-dimethyl-benznensulfonamide

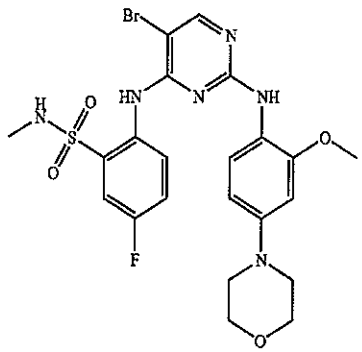


To a solution of 2-[5-Bromo-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzenesulfonamide (Ex 3-19) (1.0 g, 1.82 mmol) in DMF (10 mL), potassium carbonate (300 mg, 2.17 mmol) and iodomethane (116 μl, 1.86 mmol) are added. The resulting suspension is stirred at 50° C. for 1 h. To the reaction mixture, water is added and extracted with ethyl acetate three times. The organic layer is washed with water, dried over sodium sulfate, and concentrated in vacuo. The residue is purified by aluminum oxide column chromatography (AcOEt) to afford the title compound (728 mg, 71% yield).

NMR (400 MHz, $CDCl_3$, δ): 2.74 ((s, 6H), 3.05-3.18 (m, 4H), 3.84-3.93 (m, 4H), 3.88 (s, 3H), 6.43 (dd, 1H), 6.53 (d, 1H), 7.24 (m, 1H), 7.31 (s, 1H), 7.56 (m, 1H), 7.87 (dd, 1H), 8.05 (d, 1H), 8.21 (s, 1H), 8.49 (d, 1H), 8.49 (d, 1H), 9.27 (s, 1H). Rf: 0.23 (AcOEt:Hexane=1:1).

Example 52

Preparation of 2-[5-Bromo-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-5-fluoro-N-methyl-benzenesulfonamide



Preparation of 7-Fluoro-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,2,4]thiadiazin-3-one

To a solution of chlorosulfonylisocyanate (1.2 mL, 13.5 mmol) in nitroethane (10 mL), 4-fluoroaniline (1.0 g, 8.97 mmol) is added dropwise at 0° C. and the reaction mixture is stirred for 30 min. To the solution, aluminum chloride (1.3 g, 9.87 mmol) is added at 0° C. and the mixture is stirred at 100° C. for 1 hour. After cooling to room temperature, water is added and the mixture is extracted with ethyl acetate twice. The organic layer is washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting solids are collected by a filtration and wahed with ether to give slightly gray solids (803.9 mg, 41%).

NMR (400 MHz, DMSO-d6, δ): 7.22-7.28 (m, 1H), 7.45-7.57 (m, 1H), 7.60 (m, 1H), 11.15-11.30 (m, 1H). Rf: 0.43 (MeOH:AcOEt=1:5).

Preparation of 7-Fluoro-2-methyl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,2,4]thiadiazin-3-one

To a solution of 7-Fluoro-1,1-dioxo-1,4-dihydro-2H-1-λ⁶-benzo[1,2,4]thiadiazin-3-one (5.19 g, 24.0 mmol) in DMF (50 mL), sodium hydride (1.04 g, 26.0 mmol) and iodomethane (1.5 mL, 24.0 mmol) are added successively and the mixture is stirred for 1 hour at 70° C. After cooling to room temperature, the mixture is poured into water and the precipitate is collected by a filtration and washed with water and hexane, successively, to give slightly gray solids (5.38 g, 94%).

NMR (400 MHz, DMSO-d6, δ): 3.32 (s, 3H), 7.44 (dd, 1H), 7.75 (ddd, 1H), 7.94 (dd, 1H).

Rf (MeOH:AcOEt=1:5): 0.21. Rf: 0.39 (Hexane:AcOEt=1:1).

Preparation of 2-Amino-5-fluoro-N-methyl-benzenesulfonamide

6.79 g of 7-Fluoro-2-methyl-1,1-dioxo-1,4-dihydro-2H-1λ⁶-benzo[1,2,4]thiadiazin-3-one (29.5 mmol) is dissolved in 20% aq. sodium hydroxide and the resulting solution is stirred at 100° C. for 13.5 hours. The mixture is cooled to room temperature and poured into water. 78 mL of 5M HCl aq. is added and the precipitate is collected by a filtration and washed with water to afford slightly purple solids (3.96 g, 65%).

NMR (400 MHz, $CDCl_3$, δ): 2.60 (d, 3H), 4.55-4.82 (m, 3H), 6.74 (dd, 1H), 7.05-7.12 (m, 1H), 7.45 (dd, 1H). Rf: 0.41 (Hexane:AcOEt-1:1).

2-(5-Bromo-2-chloro-pyrimidin-4-ylamino)-5-fluoro-N-methyl -benzenesulfonamide

The reaction of pyrimidine with 2-Amino-5-fluoro-N-methyl-benzenesulfonamide is performed in the same manner described in example B.

NMR (400 MHz, $CDCl_3$, δ): 2.67 (d, 3H), 4.56 (m, 1H), 7.36-7.45 (m, 1H), 7.68 (dd, 1H), 8.39 (s, 1H), 8.42 (dd, 1H), 9.26 (s, 1H). Rf 0.59 (Hexane:AcOEt=1:1).

2-[5-Bromo-2-(2-methoxy-4-morpholin-4-yl-phenylamino) -pyrimidin-4-ylamino]-5-fluoro-N-methyl-benzenesulfonamide

The introduction of substituted aniline is performed according to the manner described in Example A.

NMR (400 MHz, $CDCl_3$, δ): 2.65 (d, 3H), 3.09-3.16 (m, 4H), 3.87 (s, 3H), 4.50 (q, 1H), 6.41 (dd, 1H), 6.52 (d, 1H), 7.25-7.33 (m, 2H), 7.69 (dd, 1H), 7.95 (d, 1H), 8.20 (s, 1H), 8.37 (dd, 1H), 8.70 (s, 1H). Rf 0.30 (Hexane:AcOEt=1:1)

Example 53

FAK Assay

All steps are performed in a 96-well black microtiter plate. Purified recombinant hexahistidine-tagged human FAK kinase domain is diluted with dilution buffer (50 mM HEPES, pH 7.5, 0.01% BSA, 0.05% Tween-20 in water) to a concentration of 94 ng/mL (2.5 nM). The reaction mixture is prepared by mixing 10 μL 5× kinase buffer (250 mM HEPES, pH 7.5, 50 μM $Na_3VO_4$, 5 mM DTT, 10 mM $MgCl_2$, 50 mM $MnCl_2$, 0.05% BSA, 0.25% Tween-20 in water), 20 μL water, 5 μL of 4 μM biotinylated peptide substrate (Biot-Y397) in aqueous solution, 5 μL of test compound in DMSO, and 5 μL of recombinant enzyme solution and incubated for 30 min at room temperature. The enzyme reaction is started by addition of 5 μL of 5 μM ATP in water and the mixture is incubated for 3 hours at 37° C. The reaction is terminated by addition of 200 μL of detection mixture (1 nM Eu-PT66, 2.5 μg/mL SA-(SL) APC, 6.25 mM EDTA in dilution buffer), and the FRET signal from europium to allophycocyanin is measured by ARVOsx+L (Perkin Elmer) after 30 min of incubation at room temperature. The ratio of fluorescence intensity of 665 nm to 615 nm is used as a FRET signal for data analysis in order to cancel the colour quenching effect by a test compound. The results are shown as percent inhibition of enzyme activity. DMSO and 0.5 M EDTA are used as a control of 0% and 100% inhibition, respectively. $IC_{50}$ values are determined by non-linear curve fit analysis using the OriginPro 6.1 program (OriginLab).

The Biot-Y397 peptide (Biotin-SETDDYAEIID ammonium salt) is designed to have the same amino acid sequence as the region from S392 to D402 of human (GenBank Accession Number L13616) and is prepared by standard methods.

Purified recombinant hexahistidine-tagged human FAK kinase domain is obtained in the following way: Full-length human FAK cDNA is isolated by PCR amplification from human placenta Marathon-Ready™ cDNA (Clontech, No. 7411-1) with the 5' PCR primer (ATGGCAGCTGCTTACCTTGAC) and the 3' PCR primer (TCAGTGTGGTCTCGTCTGCCC) and subcloned into a pGEM-T vector (Promega, No. A3600). After digestion with AccIII, the purified DNA fragment is treated with Klenow fragment. The cDNA fragment is digested with BamHI and cloned into pFastBacHTb plasmid (Invitrogen Japan K.K., Tokyo) previously cut with BamHI and Stu I. The resultant plasmid, hFAK KD (M384-G706)/pFastBacHTb, is sequenced to confirm its structure. The resulting DNA encodes a 364 amino acid protein containing a hexahistidine tag, a spacer region and a rTEV protease cleavage site at the N-terminal and the kinase domain of FAK (Met384-Gly706) from position 29 to 351.

Donor plasmid is transposed into the baculovirus genome, using MaxEfficacy DH10Bac *E.coli* cells. Bacmid DNA is prepared by a simple alkaline lysis protocol described in the Bac-to-Bac® Baculovirus Expression system (Invitrogen). Sf9 insect cells are transfected based on the protocol provided by the vendor (CellFECTIN®, Invitrogen). The expression of FAK in each lysate is analysed by SDS-PAGE and Western blotting with anti-human FAK monoclonal antibody (clone #77 from Transduction Laboratories).

The virus clone that shows the highest expression is further amplified by infection to Sf9 cells. Expression in

ExpresSF+® cells (Protein Sciences Corp., Meriden, Conn., USA) gives high level of protein with little degradation. Cell lysates are loaded onto a column of HiTrap™ Chelating Sepharose HP (Amersham Biosciences) charged with nickel sulfate and equilibrated with 50 mM HEPES pH 7.5, 0.5 M NaCl and 10 mM imidazole. Captured protein is eluted with increasing amounts of imidazole in HEPES buffer/NaCl, and further purified by dialysis in 50 mM HEPES pH 7.5, 10% glycerol and 1 mM DTT.

Example 54

Cell-Free ZAP-70 Kinase Assay

The ZAP-70 kinase assay is based on time-resolved fluorescence resonance energy transfer (FRET). 80 nM ZAP-70 are incubated with 80 nM Lck (lymphoid T-cell protein tyrosine kinase) and 4 μM ATP in ZAP-70 kinase buffer (20 mM Tris, pH 7.5, 10 μM $Na_3VO_4$, 1 mM DTT, 1 mM $MnCl_2$, 0.01% BSA, 0.05% Tween-20) for 1 hour at room temperature in a siliconized polypropylene tube. Then, the selective Lck inhibitor PP2 (1-tert-butyl-3-(4-chloro-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine; Alexis Biochemicals) is added (final concentration 1.2 μM) and incubated for further 10 min. 10 μL of this solution is mixed with the 10 μL biotinylated peptide LAT-11 (1 μM) as substrate and 20 μL of serial dilutions of inhibitors and incubated for 4 hours at room temperature. The kinase reaction is terminated with 10 μL of a 10 mM EDTA solution in detection buffer (20 mM Tris, pH 7.5, 0.01% BSA, 0.05% Tween-20). 50 μL europium-labelled anti-phosphotyrosine antibody (Eu-PT66; final concentration 0.125 nM); and 50 μL streptavidin-allophycocyanine (SA-APC; final concentration 40 nM) in detection buffer are added. After 1 hour incubation at room temperature fluorescence is measured on the Victor2 Multilabel Counter (Wallac) at 665 nm. Background values (low control) are obtained in the absence of test samples and ATP and are subtracted from all values. Signals obtained in the absence of test samples are taken as 100% (high control). The inhibition obtained in the presence of test compounds is calculated as percent inhibition of the high control. The concentration of test compounds resulting in 50% inhibition ($IC_{50}$) is determined from the dose-response curves. In this assay, the agents of the invention have $IC_{50}$ values in the range of 10 nM to 2 μM, preferably from 10 nM to 100 nM.

Recombinant ZAP-70 kinase is obtained as follows: A nucleic acid encoding full-length human ZAP-70 (GenBank #L05148) is amplified from a Jurkat cDNA library by RT-PCR and cloned into the pBluescript KS vector (Stratagene, California, USA). The authenticity of the ZAP-70 cDNA insert is validated by complete sequence analysis. This donor plasmid is then used to construct a recombinant baculovirus transfer vector based on the plasmid pVL1392 (Pharmingen, California, USA) featuring in addition an N-terminal hexahistidine tag. Following co-transfection with AcNPV viral DNA, 10 independent viral isolates are derived via plaque-purification, amplified on small scale and subsequently analyzed for recombinant ZAP-70 expression by Western Blot using a commercially available anti-ZAP-70 antibody (Clone 2F3.1, Upstate Biotechnology, Lake Placid, N.Y., USA). Upon further amplification of one positive recombinant plaque, titrated virus stocks are prepared and used for infection of Sf9 cells grown in serum-free SF900 II medium (Life Technologies, Basel, Switzerland) under defined, optimized conditions. ZAP-70 protein is isolated from the lysate of infected Sf9 cells by affinity chromatography on a Ni-NTAcolumn (Qiagen, Basel, Switzerland).

Recombinant His-tagged ZAP-70 is also available from PanVera LLC, Madison, Wis., USA.

LAT-11 (linker for activation of T cell): The biotinylated peptide LAT-11 (Biotin -EEGAPDYENLQELN) used as a substrate in the ZAP-70 kinase assay is prepared in analogy to known methods of peptide synthesis. The N-α Fmoc group of Fmoc-Asn(Trt)-oxymethyl-4-phenoxymethyl-co(polystyrene-1%-divnyl-benzene), content of Asn approx. 0.5 mmol/g, is cleaved using piperidine, 20% in DMF. Four equivalents per amino-group of Fmoc-amino acid protected in their side chains [Asp(OtBu), Glu(OtBu), Asn(Trt), Gln(Trt) and Tyr (tBu)] are coupled using DIPCDI and HOBt in DMF. After complete assembly of the peptide chain the terminal Fmoc-protecting group is removed with piperidine in DMF as before. L(+)-biotinyl -aminohexanoic acid is then coupled to the terminal amino group using DIPCDI and HOBt in DMF using four equivalents of the reagents for four days at RT. The peptide is cleaved from the resin support and all side-chain protecting groups are simultaneously removed by using a reagent consisting of 5% dodecylmethylsulfide and 5% water in TFA for two hours at RT. Resin particles are filtered off, washed with TFA and the product is precipitated from the combined filtrates by the addition of 10 to 20 volumes of diethyl ether, washed with ether and dried. The product is purified by chromatography on a C-18 wide-pore silica column using a gradient of acetonitrile in 2% aqueous phosphoric acid. Fractions containing the pure compound are collected, filtered through an anion-exchange resin (Biorad, AG4-X4 acetate form) and lyophilized to give the title compound. MS: 1958.0 $(M-H)^{-1}$

Example 55

Phosphorylation Levels of FAK

Phosphorylation levels of FAK at Tyr397 is quantified by the sandwich ELISA. Mouse mammary carcinoma 4T1 cells ($1\times10^5$) are plated in wells of 96-well culture plates and incubated with or without various concentrations of inhibitors for 1 h in Dulbecco's modified eagle medium containing 0.5% BSA. The medium is removed and cells are lysed in 200 AIL 50 mM Tris-HCl, pH 7.4, containing 1% NP-40, 0.25% sodium deoxycholate, 150 mM NaCl, 1 mM EDTA, 1 mM PMSF, 1 mM $Na_3VO_4$, 1 mM NaF, 1 μg/mL aprotinin, 1 μg/mL leupeptin and 1 μg/mL pepstatin. After centrifugation, the supernatants are subjected to a sandwich ELISA to quantify the phosphorylated FAK and total FAK. Cell lysates are applied to 96-well flat-bottom ELISA plates which have been pre-coated with 100 μL/well of 4 μg/mL mouse monoclonal anti -FAK antibody (clone 77, Becton Dickinson Transduction Laboratories) in 50 mM Tris-HCl, pH 9.5, containing 150 mM NaCl for 18 h at 4° C. and blocked with 300 μL of BlockAce (Dainippon Pharmaceuticals Co.) diluted at 1:4 with $H_2O$ at room temperature for 2 h. After washing with TBSN (20 mM Tris-HCl, pH 8.3, containing 300 mM NaCl, 0.1% SDS and 0.05% NP-40), total FAK is detected with 100 μL of 1 μg/ml anti-FAK polyclonal antibody (#65-6140, Upstate Biology Inc.), and phosphorylated FAK is detected with 100 μL of 0.25 μg/μL anti-phosphorylated FAK (Y397) antibody (Affinity BioReagents, #OPA1-03071) in BlockAce diluted at 1:10 with $H_2O$. After 1 h incubation at room temperature, plates are washed with TBSN and 100 μL of biotinylated anti-rabbit IgG (#65-6140, Zymed Laboratolies Inc.) diluted at 1:2000 with BlockAce diluted at 1:10 with $H_2O$ is incubated at room temperature for 1 h. After washing with TBSN, ABTS solution substrate kit (#00-2011, Zymed Lobolatories Inc.) is used for color development. Absorbance at

405 nm is measured after 20 min incubation at room temparature. The concentration of compound causing 50% reduction of phosphorylation level of FAK is determined.

Example 56

Anchorage-Independent Tumor Cell Growth Assay

Mouse mammary carcinoma 4T1 cells ($5\times10^3$) are plated in 96-well Ultra low Attachment plates (#3474, Corning Inc.) in 100 µL of Dulbecco's modified eagle medium containing 10% FBS. Cells are cultured for 2 h and inhibitors are added at various concentrations in a final concentration of 0.1% DMSO. After 48 h, cell growth is assayed with the cell counting kit-8 (Wako Pure Chemical), which uses a water soluble tetrazolium salt WST8. Twenty µL of the reagent is added into each well and cells are further cultured for 2 h. The optical density is measured at 450 nm. The concentration of compound causing 50% inhibition of growth is determined.

Example 57

In Vitro T Cell Migration Assay

Inhibitory activities of FAK inhibitors on the mobility of immune cells are secured by the following in vitro study. That is, Jurkat T human leukemic cell line are placed at $1\times10^5$ cells in the upper chamber of Fluoroblok with 8 µm pores (Beckton Dickinson, UK), and are allowed to migrate by four hours cultivation at 37° C., in 95% air-5% $CO_2$ depending on a concentration gradient of fetal bovine serum (10% FBS). Cell mobility is appraised through the number of cells migrated into lower chamber by labeling with calcein-AM (Molecular Probes, Netherlands) at 8 µg/ml in HBSS for 1 h. For evaluation of FAK inhibitors, both the upper and lower chambers are added with various concentrations of FAK inhibitors (0.03-1 µM). IC50 values are calculated by the decrement of those fluorescent intensity compared to that in vehicle-treated group measured with Ascent (Ex: 485 nm, Em: 538 nm).

Example 58

Test for Activity Against IGF-I Induced IGF-IR Autophosphorylation Using the Cellular "Capture ELISA" Test

The assay is conducted as follows:

For the assay NIH-3T3 mouse fibroblasts transfected with human IGF-R cDNA (complete human IGF-R cDNA: GenBank Acc. No. NM_000875), prepared as described in Kato et al., J. Biol. Chem. 268, 2655-61, 1993, are used. The cells which overexpress human IGF-R are cultured in Dulbecco's minimal essential (DMEM) medium, containing 10% Fetal Calf Serum (FCS). For the assay 5,000 cells/well are plated on day 1 on 96-well plates (Costar #3595) in normal growth medium and incubated for 2 days at 37° C. in a standard $CO_2$ cell incubator. The density of the cells does not exceed 70-80% at day 3. On day 3 the medium is discarded and the cells are incubated for 24 h in minimal medium (DMEM, containing 0.5% FCS). Compounds of formula I [starting from 10 mM dimethyl sulfoxide (DMSO) stock solutions] are added to produce final concentrations of 0.01, 0.03, 0.1, 0.3, 1, 3 and 10 µM to determine the $IC_{50}$ value. The cells are incubated for 90 min in the presence of a compound of formula I. Thereafter the cells are stimulated with 50 µl IGF-I (final concentration of IGF-I in the well=10 ng/ml; IGF-I is obtained from Sigma; Product Code: 13769) and incubated for 10 min at 37° C.

The medium is discarded and the cells are washed twice with PBS/O (=Phosphate-Buffered Saline without $CaCl_2$) and lysed for 15 min on ice with 50 µl/well RIPA -buffer [50 mM Tris-HCl, pH=7.2, 120 mM NaCl, 1 mM EDTA, 6 mM EGTA, 1% NP40, 20 mM NaF, 1 mM benzamidine, 15 mM sodium pyrophosphate, 1 mM Phenyl methyl sulphonyl fluoride (PMSF) and 0.5 mM $Na_3VO_4$] and shaken for 10 min using a 96-well plate shaker (=cellular extracts).

Packard HTRF-96 black plates are coated with 50 µl IGF-IR monoclonal Antibody (mAB) (Santa Cruz; Cat. No.: SC-462) in a concentration of 5 µg/ml at 4° C. overnight. The plates are washed twice with 0.05% (v/v) Tween-20 in Phosphate-Buffered Saline (PBS) and once with nanopure $H_2O$. Blocking is done for 2 h at room temperature (RT) with 3% Bovine Serum Albumin (BSA) in TBS-T buffer (20 mM Tris-HCl, pH=7.6, 137 mM NaCl, 0.05% Tween-20). After blocking, the plates are washed once with nanopure $H_2O$.

Cellular extracts (40 µl/well) are pipetted onto the precoated Packard plates, together with 40 µl of the anti-phosphotyrosine mouse mAB PY-20 conjugated with Alkaline Phosphatase (AP) (1:1000 diluted in RIPA buffer; the antibody is obtained from Transduction Labs; Cat. No.: P11120).

After incubating the extracts and the secondary antibody for 2 h at 4° C., the extracts are discarded, the plates are washed twice with 0.05% (v/v) Tween-20 in PBS and once with nanopure water.

90 µl/well AP substrate (CDP-Star; obtained from Tropix; Cat. No.: MS100RY) are then added and the plates are incubated for 45 min at RT in the dark, followed by measuring AP activity in a Packard Top Count Microplate Scintillation Counter. The $IC_{50}$ values for the compounds of formula I are calculated via linear regression analysis using the GraphPad Instat program (GraphPad Software, USA). $IC_{50}$ values in the range of 5 nM to 1 µM, especially in the range of 5 nM to 300 nM are found.

Example 59

In Vivo Activity in the Nude Mouse Xenograft Model

female or male BALB/c nude mice (5-8 weeks old, Charles River Japan, Inc., Yokohama, Japan) are kept under sterile conditions with water and feed ad libitum. Tumours are induced by subcutaneous injection of tumour cells (human epithelial cell line MIA PaCa-2; European Collection of Cell Cultures (ECACC), Salisbury, Wiltshire, UK, Catalogue Number 85062806; cell line from a 65 year old Caucasian male; undifferentiated human pancreatic carcinoma cell line) into left or right flank of mice under Forene® anaesthesia (Abbott Japan Co., Ltd., Tokyo, Japan). Treatment with the test compound is started when the mean tumor volumes reached approximately 100 $mm^3$. Tumour growth is measured two times per week and 1 day after the last treatment by determining the length of two perpendicular axis. The tumour volumes are calculated in accordance with published methods (see Evans et al., Brit. J. Cancer 45, 466-8, 1982). The anti-tumour efficacy is determined as the mean increase in tumour volume of the treated animals divided by the mean increase in tumour volume of the untreated animals (controls) and, after multiplication by 100, is expressed as delta T/C [%]. Tumour regression is reported as the mean changes of tumor volume of the treated animals divided by the mean tumor volume at start of treatment and, after multiplication by

100, is expressed as regression [%]. The test compound is orally administered daily with or without drug holidays.

As an alternative to cell line MIA PaCa-2, another cell line may also be used in the same manner, for example:

the 4T1 breast carcinoma cell line (ATCC Number CRL-2539; see also Cancer. 88(12 Supple), 2979-2988, 2000) with female BALB/c mice (injection into mammary fat pad).

On the basis of these studies, a compound of formula I according to the invention shows therapeutic efficacy especially against proliferative diseases responsive to an inhibition of a tyrosine kinase.

## Example 60

### Tablets

Tablets comprising 50 mg of active ingredient, for example one of the compounds of formula I described in Examples 1 to 131, and having the following composition are prepared in customary manner

Composition:

| | |
|---|---|
| active ingredient | 50 mg |
| wheat starch | 150 mg |
| lactose | 125 mg |
| colloidal silicic acid | 12.5 mg |
| talc | 22.5 mg |
| magnesium stearate | 2.5 mg |
| Total: | 362.5 mg |

Preparation: The active ingredient is mixed with a portion of the wheat starch, with the lactose and the colloidal silicic acid and the mixture is forced through a sieve. A further portion of the wheat starch is made into a paste, on a water bath, with five times the amount of water and the powder mixture is kneaded with the paste until a slightly plastic mass is obtained.

The plastic mass is pressed through a sieve of about 3 mm mesh size and dried, and the resulting dry granules are again forced through a sieve. Then the remainder of the wheat starch, the talc and the magnesium stearate are mixed in and the mixture is compressed to form tablets weighing 145 mg and having a breaking notch.

## Example 61

### Soft Capsules

5000 soft gelatin capsules comprising each 50 mg of active ingredient, for example one of the compounds of formula I described in Examples 1 to 131, are prepared in customary manner

Composition:

| | |
|---|---|
| active ingredient | 250 g |
| Lauroglykol | 2 litres |

Preparation: The pulverized active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer to a particle size of approx. 1 to 3 μm. 0.419 g portions of the mixture are then dispensed into soft gelatin capsules using a capsule-filling machine.

Biological Results:

| Example | FAK IC50 (nM) | Phos IC50 (μM) | Growth IC50 (μM) | T Cell Migration IC50 (μM) | IGF-1R IC50 (μM) |
|---|---|---|---|---|---|
| 1.00 | 140 | 0.7 | >10 | | |
| 2.00 | 13 | 1.2 | | | |
| 3.01 | 44 | 0.34 | >10 | | |
| 3.02 | 36 | 0.85 | 4 | | |
| 3.03 | 9.1 | 0.14 | 0.8 | | |
| 3.04 | 32 | 0.53 | 2 | | |
| 3.05 | 21 | 0.17 | 2 | | >10 |
| 3.06 | 13 | 0.11 | 2 | | |
| 3.07 | 16 | 0.45 | 2 | | |
| 3.08 | 74 | 0.3 | 6 | | |
| 3.09 | 48 | 0.5 | 0.7 | | |
| 3.10 | 52 | 0.95 | >10 | | |
| 3.11 | 9 | 0.04 | 0.3 | | 0.2 |
| 3.12 | 5.4 | 0.01 | 1 | | |
| 3.13 | 58 | 1.7 | 0.6 | | 0.74 |
| 3.14 | 54 | 0.4 | 5 | | |
| 3.15 | 7 | 0.02 | 0.8 | | 0.94 |
| 3.16 | 48 | 1.1 | 3 | | |
| 3.17 | 2.8 | 0.03 | 0.2 | | <0.08 |
| 3.18 | 130 | 1.5 | 9 | | |
| 3.19 | 6.8 | 0.35 | 0.8 | | 0.1 |
| 3.20 | 16 | 0.22 | 0.3 | | |
| 3.22 | 120 | 0.9 | 2 | | |
| 3.23 | 38 | 0.39 | 0.5 | | |
| 3.24 | 64 | 3.5 | 5 | | |
| 3.25 | 22 | 0.3 | 0.3 | | 0.81 |
| 3.26 | 50 | 0.79 | 2 | | |
| 3.28 | 43 | 0.71 | 0.7 | | |
| 3.29 | 89 | 0.6 | >10 | | |
| 3.30 | 69 | 0.6 | 3 | | |
| 3.31 | 13 | 1.1 | 5 | | |
| 3.32 | 14 | 0.18 | 0.49 | 0.28 | 0.12 |
| 3.33 | 2.9 | 0.03 | 0.05 | 0.09 | 0.13 |
| 3.34 | 7 | 0.1 | 0.24 | 0.13 | <0.08 |
| 3.35 | 13 | 0.02 | 0.17 | 0.8 | 3.55 |
| 3.36 | 43 | 1.8 | 2.8 | | |
| 3.37 | 39 | 1.1 | 2.6 | | |
| 3.38 | 64 | 1.7 | 3.8 | | |
| 3.39 | 2 | 0.02 | 0.03 | 1 | 0.09 |
| 3.40 | 9 | >10 | 0.9 | | |
| 3.41 | 22 | >10 | 0.43 | | |
| 3.42 | 29 | 0.35 | 0.3 | | |
| 3.43 | 5.6 | 0.2 | 0.11 | | 0.27 |
| 3.44 | 11 | 0.05 | 0.09 | | 0.09 |
| 3.45 | 0.9 | 0.02 | 0.02 | | |
| 3.46 | 4 | 0.1 | 0.18 | 0.3 | |
| 3.47 | 1 | 0.1 | 0.06 | | |
| 3.48 | 7 | 0.07 | 0.3 | | 0.21 |
| 3.49 | 39 | 10 | 0.39 | | |
| 3.50 | 13 | 0.12 | 1 | | 1.19 |
| 3.51 | 29 | 0.2 | 0.4 | | 0.41 |
| 3.52 | 29 | 0.42 | 2 | | |
| 3.53 | 6 | 0.07 | 0.21 | | |
| 3.54 | 0.9 | 0.01 | 0.07 | | <0.08 |
| 3.55 | 34 | >10 | 3 | | |
| 3.56 | 28 | 0.53 | 0.15 | | |
| 3.57 | 28 | 0.61 | 3 | | |
| 3.58 | 21 | 0.08 | 0.3 | | 0.14 |
| 3.59 | 95 | 1.2 | >10 | | |
| 3.60 | 90 | 0.93 | 2 | | |
| 3.61 | 12 | 10 | >10 | | |
| 3.62 | 63 | >10 | >10 | | |
| 3.63 | 27 | >10 | >10 | | |
| 3.64 | 5 | 0.13 | 0.7 | 0.21 | |
| 3.65 | 8 | 0.08 | 0.1 | | 0.15 |
| 3.66 | 1 | 0.08 | 0.07 | | 0.25 |
| 3.67 | 6 | 0.38 | 0.39 | | |
| 3.68 | 5.5 | 0.2 | 0.63 | 1 | |
| 3.69 | 4 | 0.2 | 0.11 | 0.58 | |
| 3.70 | 3.5 | 0.02 | 0.13 | | |
| 3.71 | 11 | 0.05 | 0.08 | | |
| 3.72 | 2.1 | 0.11 | 0.06 | | |
| 3.73 | 11 | 0.03 | 0.29 | | 1.63 |

-continued

| Example | FAK IC50 (nM) | Phos IC50 (μM) | Growth IC50 (μM) | T Cell Migration IC50 (μM) | IGF-1R IC50 (μM) |
|---|---|---|---|---|---|
| 3.74 | 15 | 0.1 | 0.15 | | |
| 3.75 | 72 | 0.5 | 1.3 | | |
| 3.76 | 15 | 0.29 | 1.3 | 0.7 | |
| 3.77 | 65 | >10 | 3 | | |
| 3.78 | 10 | >10 | 0.22 | | |
| 3.79 | 5 | 1.3 | 0.12 | | |
| 3.80 | 12 | 0.22 | 0.45 | | 5 |
| 3.81 | 21 | 0.52 | 0.98 | | >10 |
| 3.82 | 4.8 | 0.2 | 0.07 | | |
| 3.83 | 20 | 0.08 | 0.32 | | 0.68 |
| 3.84 | 10 | 1 | 0.08 | | |
| 6.00 | 110 | 0.35 | 5 | | |
| 7.00 | 5.3 | 0.21 | 0.47 | 0.04 | 0.19 |
| 7.01 | 4.7 | 0.6 | 0.54 | | 0.19 |
| 7.02 | 7.5 | 0.1 | 0.36 | | 0.77 |
| 7.03 | 2.9 | 0.3 | 0.39 | | 0.27 |
| 7.04 | 5.2 | 1 | 0.29 | | |
| 7.05 | 6.2 | 0.3 | 0.2 | | 0.25 |
| 7.06 | 17 | 0.8 | 1.09 | 0.25 | |
| 7.07 | 4.1 | 0.9 | 0.18 | | |
| 7.08 | 8.7 | 0.8 | 1 | | |
| 7.09 | 8.2 | 1 | 0.85 | | |
| 7.10 | 6.6 | 1 | 0.98 | | |
| 7.11 | 2.5 | 0.6 | 1.2 | | 0.77 |
| 7.12 | 1.9 | 0.9 | 1 | 0.31 | 0.62 |
| 7.13 | 5.5 | 0.8 | 1.22 | | |
| 7.14 | 7.6 | 0.3 | 0.36 | | 0.33 |
| 7.15 | 4.5 | 0.06 | 0.19 | | 0.26 |
| 7.16 | 6.4 | 0.2 | 0.42 | | |
| 7.17 | 4.3 | 0.7 | 0.69 | | |
| 7.18 | 6.2 | 0.5 | 0.7 | | |
| 7.19 | 13 | | 0.33 | | |
| 7.20 | 2.5 | >10 | 0.11 | | |
| 7.21 | 3.3 | >10 | 0.46 | | |
| 7.22 | 25 | | 0.48 | | |
| 7.23 | 1.4 | | 0.25 | | |
| 7.24 | 5.1 | | 0.09 | | |
| 7.25 | 13 | 0.2 | 0.73 | | |
| 7.25 | 2 | >10 | 0.57 | | |
| 7.26 | 4.1 | | 0.15 | | |
| 7.27 | 21 | 0.5 | 0.22 | | |
| 7.28 | 34 | 1 | 0.15 | | |
| 7.29 | 57 | 2 | 0.48 | | |
| 7.30 | 2.1 | | 0.3 | 1 | |
| 8.01 | 6.6 | 0.6 | 0.33 | | |
| 8.02 | 2.4 | 0.5 | 0.99 | | |
| 8.03 | 13 | 0.22 | 1 | | >10 |
| 8.04 | 8 | >10 | 1.1 | | |
| 9.01 | 22 | 0.36 | 1 | 0.6 | |
| 9.02 | 15 | 0.5 | 0.81 | | |
| 9.03 | 18 | 0.1 | 0.37 | | |
| 9.04 | 13 | 0.2 | 0.73 | | |
| 9.05 | 22 | 0.36 | 1.6 | | 0.6 |
| 9.06 | 23 | 3 | 0.4 | 0.3 | |
| 9.07 | 17 | >10 | 0.26 | | |
| 10.01 | 39 | 1 | 0.44 | | |
| 10.02 | 26 | 0.9 | 1.06 | | |
| 10.03 | 23 | 0.9 | 2.4 | | |
| 11.01 | 9 | 0.7 | 0.85 | | |
| 11.02 | 4.1 | 0.8 | 0.69 | | |
| 11.03 | 26 | 0.41 | 0.1 | | |
| 11.04 | 4.3 | >10 | 3.2 | | |
| 12.01 | 2.5 | 0.09 | 0.4 | 0.22 | |
| 12.02 | 1.6 | | 0.05 | | |
| 12.03 | 2.3 | | 0.25 | | |
| 12.04 | 1.1 | | 0.14 | | |
| 12.06 | 2.6 | | | | |
| 13.01 | 65 | | 0.81 | | |
| 14.01 | 19 | 0.2 | 1.47 | 0.28 | |
| 14.02 | 190 | 2 | 1.1 | 1 | |
| 14.03 | 30 | 10 | 1.01 | | |
| 14.04 | 18 | | 0.54 | | |
| 14.05 | 37 | >10 | 1 | | |
| 14.06 | 63 | 10 | 1.11 | | |
| 14.07 | 7.5 | 0.2 | 1.4 | | |
| 15.01 | 15 | 10 | 0.47 | | |

-continued

| Example | FAK IC50 (nM) | Phos IC50 (μM) | Growth IC50 (μM) | T Cell Migration IC50 (μM) | IGF-1R IC50 (μM) |
|---|---|---|---|---|---|
| 15.02 | 21 | >10 | 0.66 | | |
| 15.03 | 44 | 2 | 1.67 | | |
| 16.01 | 44 | >10 | 4 | | |
| 16.02 | 6 | >10 | 0.6 | | |
| 16.03 | 21 | 3 | >10 | | |
| 16.04 | 9.5 | >10 | 0.92 | | |
| 16B | 11 | 3 | 7 | | |
| 16.C | 28 | 0.9 | >10 | | |
| 18.01 | 19 | >10 | 1.29 | | |
| 19.01 | <1 | 0.2 | 0.3 | 0.29 | 1.41 |
| 19.02 | 1.6 | 0.13 | 0.38 | | 0.91 |
| 19.03 | <1 | 0.3 | 0.09 | | 0.64 |
| 19.04 | 1.6 | 0.2 | 0.34 | | 0.14 |
| 19.05 | 1.8 | 0.2 | 0.67 | 0.07 | 0.47 |
| 19.06 | 5 | 1 | 0.7 | | |
| 19.07 | 2.1 | 0.3 | 0.11 | | |
| 19.08 | 3.2 | 0.03 | 0.4 | 0.29 | 0.13 |
| 19.09 | 1.3 | 0.17 | 0.39 | 0.3 | 0.48 |
| 19.10 | 1.3 | 0.06 | 0.56 | | 1.02 |
| 19.11 | 38 | >10 | 2 | | |
| 19.12 | 9 | >10 | 0.7 | | 0.63 |
| 19.13 | 2.5 | 0.3 | 1.1 | | |
| 19.14 | 2.6 | 0.4 | 1.13 | | 0.44 |
| 19.15 | 3.1 | 0.5 | 0.36 | | |
| 19.16 | 2.3 | 0.7 | 1.1 | | |
| 19.17 | 1 | >10 | 0.17 | | |
| 19.18 | 7 | 0.13 | 0.87 | | |
| 19.19 | 5.7 | | 0.4 | | |
| 19.20 | 1.6 | 0.03 | 0.07 | | 0.23 |
| 19.21 | 84 | >10 | 1.71 | | |
| 19.22 | 3.4 | 0.12 | 0.51 | | |
| 19.23 | 6.4 | 0.7 | 0.71 | | |
| 19.24 | 1.8 | 0.05 | 0.12 | | |
| 19.25 | 7.2 | 1 | 0.49 | | 0.24 |
| 19.26 | 6.1 | 0.1 | 0.3 | | |
| 19.27 | 1.5 | 0.3 | 0.4 | | |
| 19.28 | 4.8 | 0.1 | 0.12 | 0.3 | 0.46 |
| 19.29 | 1.9 | | | | |
| 19.30 | <1 | 0.06 | 0.1 | | |
| 19.31 | 1.8 | 0.4 | 0.38 | | |
| 19.32 | 1.4 | 0.2 | 0.31 | | |
| 20.01 | 10 | 0.3 | 0.18 | 0.25 | 0.7 |
| 20.02 | 9 | 0.12 | 0.17 | 0.75 | 0.52 |
| 20.03 | 42 | 0.4 | 2.5 | | 2.78 |
| 20.04 | 23 | 0.58 | 1.9 | | |
| 20.05 | 6.8 | 0.87 | 1.46 | | |
| 20.06 | 5 | 0.36 | 0.14 | 49 | |
| 20.07 | 3 | 0.1 | 0.05 | | 0.38 |
| 20.08 | 6.8 | 0.17 | 0.05 | 0.29 | |
| 20.09 | 2 | 0.3 | 0.01 | | |
| 20.10 | 2 | 0.1 | 0.02 | | |
| 20.11 | 26 | 2 | 0.4 | | |
| 20.12 | 9.5 | | | | |
| 20.13 | 6.3 | | 0.04 | | |
| 20.14 | 33 | | 0.32 | | |
| 20.15 | 14 | 0.4 | 0.97 | 0.3 | |
| 20.16 | 7.5 | | 0.06 | | |
| 20.17 | 2 | | 0.14 | | |
| 20.18 | 15 | | 0.81 | | |
| 20.19 | 28 | | 0.21 | | |
| 20.20 | 3.12 | | | | 0.1 |
| 20.21 | 26 | 3 | 0.68 | | |
| 20.22 | 8 | >10 | 0.19 | | |
| 20.23 | 30 | 0.49 | 3 | | |
| 20.24 | 19 | 0.48 | 2 | | |
| 20.25 | 6.2 | 0.21 | 0.06 | | |
| 20.26 | 5.3 | 0.76 | 0.27 | | |
| 20.27 | 12 | 0.85 | 0.05 | | 0.29 |
| 20.28 | 9.2 | 0.17 | 0.08 | | 0.42 |
| 20.29 | 6.1 | 0.2 | 0.05 | | 0.31 |
| 20.30 | 7.6 | 0.3 | 0.08 | | 0.67 |
| 20.31 | 39 | | 0.5 | | |
| 20.32 | 13 | | 0.11 | | |
| 20.33 | 2.5 | | 0.38 | | |
| 20.34 | 13 | 1 | 0.12 | | |
| 20.35 | 8.7 | 0.09 | 0.09 | | 0.15 |

-continued

| Example | FAK IC50 (nM) | Phos IC50 (μM) | Growth IC50 (μM) | T Cell Migration IC50 (μM) | IGF-1R IC50 (μM) |
|---|---|---|---|---|---|
| 21.01 | 1 | 0.07 | 0.19 | | 0.47 |
| 21.02 | 8.5 | 0.33 | >10 | | |
| 21.03 | 1.7 | 0.3 | 0.3 | | |
| 21.04 | 1.8 | 0.05 | 0.3 | | |
| 22.01 | 43 | >10 | >10 | | |
| 22.02 | 26 | 1 | 3 | | |
| 22.03 | 6.6 | 0.09 | 0.15 | | 0.26 |
| 23.01 | 3.4 | 0.6 | 0.2 | 0.63 | 0.53 |
| 23.02 | 1.5 | 0.2 | 0.4 | | 0.8 |
| 23.03 | 1.7 | 1 | 1.12 | | 0.82 |
| 23.04 | 1.2 | 0.9 | 1.07 | | 0.6 |
| 23.05 | 1.9 | >10 | 0.59 | | |
| 23.06 | 16 | 1 | 0.57 | | |
| 23.07 | 2.1 | 3 | 0.84 | | |
| 23.08 | 6.7 | 0.3 | 0.49 | | |
| 23.09 | 2.1 | 0.2 | 0.28 | | |
| 24.01 | 3.6 | 0.11 | 0.44 | | 0.05 |
| 24.02 | 2.1 | 0.5 | 0.11 | | 0.39 |
| 24.03 | 1 | 0.3 | 1.08 | | |
| 25.01 | 8.5 | 3 | 1 | | |
| 25.02 | 3 | 0.4 | 0.13 | | 0.64 |
| 26.01 | 4.4 | 0.05 | 0.35 | | 0.29 |
| 26.02 | 1.9 | 0.03 | 0.12 | 0.09 | 0.39 |
| 26.03 | 1.4 | 0.1 | 0.13 | | 0.23 |
| 26.04 | 4.9 | 0.05 | 0.43 | 0.29 | 1.16 |
| 26.05 | 2.1 | 0.09 | 0.23 | | 1.5 |
| 26.06 | 4.4 | 0.1 | 0.35 | | |
| 26.07 | 11 | 0.5 | 0.95 | | |
| 26.08 | 2.9 | 0.01 | 0.18 | | |
| 26.09 | 2.3 | 0.04 | 0.22 | | |
| 26.10 | 2 | 0.01 | 0.14 | | |
| 26.11 | 4.4 | 0.4 | 0.78 | 0.5 | |
| 26.12 | 3.7 | 0.2 | 0.19 | | |
| 26.13 | 1.6 | 0.2 | 0.44 | | |
| 26.14 | 5 | | 0.19 | | |
| 26.15 | 6.9 | 1.2 | 0.08 | | 0.07 |
| 26.16 | 9 | 0.32 | 2 | | |
| 26.17 | 17 | 0.3 | 0.1 | 0.26 | |
| 26.18 | 1.3 | 6 | 1.17 | | |
| 26.19 | 9.2 | 0.43 | 0.79 | | |
| 26.20 | 10 | 0.14 | 0.22 | 0.6 | 0.49 |
| 26.21 | 1.1 | 0.1 | 0.49 | | |
| 26.22 | <1 | 0.1 | 0.28 | | |
| 26.23 | 1.4 | 0.3 | 0.09 | 0.3 | 0.18 |
| 26.24 | 1 | 0.5 | 0.48 | 0.9 | |
| 26.25 | <1 | 0.6 | 0.73 | 0.3 | |
| 26.26 | 1.9 | 0.2 | 0.07 | | 0.34 |
| 26.27 | 4.8 | 0.6 | 1.49 | | |
| 26.28 | 2.1 | 0.5 | 1.52 | | |
| 26.29 | <1 | 0.31 | 0.26 | | |
| 26.30 | 4.4 | 1 | 0.76 | | |
| 26.31 | 2 | 0.3 | 0.16 | | |
| 26.32 | 1.6 | | 0.05 | 0.6 | |
| 26.33 | 4 | | 0.06 | 0.23 | |
| 26.34 | 7 | | 0.1 | 0.25 | |
| 26.35 | 4.5 | | 0.05 | 0.3 | |
| 26.36 | 1.9 | | 0.07 | 0.09 | |
| 26.37 | <1 | | | | |
| 26.38 | <1 | | | | |
| 26.39 | 3.1 | | | | |
| 27.01 | 14 | 0.06 | 0.47 | | |
| 27.02 | 5.1 | 0.5 | 1.1 | | |
| 27.03 | 6.3 | >10 | 0.56 | | |
| 27.04 | 11 | 0.1 | 0.27 | | |
| 27.05 | 8.2 | 0.04 | 0.3 | | |
| 27.06 | 1 | 0.08 | 0.31 | | |
| 27.07 | 5.5 | 2 | 0.57 | | |
| 27.08 | 9.3 | 0.6 | 0.75 | | |
| 27.09 | 4.2 | 0.5 | 0.36 | | |
| 28.01 | 12 | 0.3 | 0.46 | | 0.3 |
| 28.02 | 1.9 | 0.08 | 0.44 | | 3.71 |
| 28.03 | 7.4 | 0.07 | 0.29 | | |
| 28.04 | 7.5 | 0.3 | 0.3 | | |
| 28.05 | 6.7 | 0.1 | 0.12 | | 1.39 |
| 28.06 | 17 | 0.6 | 0.56 | | |
| 28.07 | 47 | 3 | >10 | | |

-continued

| Example | FAK IC50 (nM) | Phos IC50 (μM) | Growth IC50 (μM) | T Cell Migration IC50 (μM) | IGF-1R IC50 (μM) |
|---|---|---|---|---|---|
| 28.08 | 4.6 | 0.4 | 0.37 | | |
| 28.09 | 3.1 | 0.5 | 0.36 | | |
| 28.10 | 20 | 3 | 1.85 | | |
| 28.11 | 4.2 | 0.5 | 0.63 | | |
| 28.12 | 3.2 | 0.3 | 0.43 | | 0.1 |
| 28.13 | 7.8 | 0.1 | 0.55 | 0.29 | |
| 28.14 | 3 | 0.1 | 1.44 | | |
| 28.15 | 10 | 0.5 | 0.69 | | |
| 28.16 | 11 | 0.11 | 1 | 0.6 | |
| 28.17 | 15 | 0.16 | 1.9 | | |
| 28.18 | 9.1 | >10 | 2.03 | | |
| 28.19 | 3.7 | 0.5 | 0.14 | | |
| 28.20 | 4.4 | 2 | 0.4 | | |
| 28.21 | 1.3 | 0.1 | 0.23 | | |
| 28.22 | 1.3 | 0.1 | 0.3 | | |
| 28.23 | 5.9 | 0.5 | 0.28 | | |
| 28.24 | 2.9 | 0.2 | 0.09 | | 2.57 |
| 28.25 | 3.9 | 0.04 | 0.13 | | |
| 28.26 | 6.6 | 0.2 | 0.57 | | |
| 28.27 | 2.4 | 0.3 | 0.42 | 0.5 | |
| 28.28 | 5.2 | 0.4 | 0.52 | 1 | |
| 28.29 | 11 | 0.4 | 0.36 | | |
| 28.30 | 2.3 | 0.9 | 0.11 | | |
| 28.31 | 7.4 | 0.06 | 1.06 | | |
| 29.01 | 13 | 0.7 | 2.2 | | 0.09 |
| 29.02 | 3.3 | 0.7 | 1.1 | | |
| 29.03 | 5.6 | 0.1 | 0.99 | | |
| 30.01 | 22 | 0.2 | 0.89 | | |
| 30.02 | 12 | 0.2 | 0.47 | | |
| 30.03 | 19 | 0.5 | 0.68 | | |
| 30.04 | 25 | 0.3 | 0.99 | | |
| 30.05 | 8.5 | 2 | 0.29 | | |
| 30.06 | 15 | 1 | 1.03 | | |
| 30.07 | 8.8 | 0.6 | 0.47 | | |
| 31.01 | 30 | >10 | 1.6 | | |
| 31.02 | 31 | 0.28 | 0.29 | | 0.42 |
| 32.01 | 4.1 | 0.1 | 0.29 | | |
| 32.02 | 5.9 | 0.05 | 0.37 | | 0.12 |
| 33.01 | 2.5 | 0.08 | 0.25 | | |
| 33.02 | 5.2 | 0.06 | 0.25 | | 0.1 |
| 34.01 | 8 | 0.1 | 0.37 | | 0.28 |
| 34.02 | 11 | 0.08 | 1.17 | | |
| 34.03 | 33 | 0.19 | 2.25 | | |
| 34.04 | 13 | >10 | 1.22 | | |
| 34.05 | 51 | 0.36 | 5.1 | | |
| 34.06 | 14 | >10 | 3 | | |
| 34.07 | 27 | >10 | 2.7 | | |
| 34.08 | 8.7 | >10 | 1.9 | | |
| 35.01 | 6.8 | >10 | 1.43 | | |
| 35.02 | 6.1 | 0.7 | 0.23 | | |
| 51.00 | 8.1 | 0.013 | 0.19 | | 0.2 |
| 52.00 | 13 | 0.2 | 0.41 | | <0.08 |

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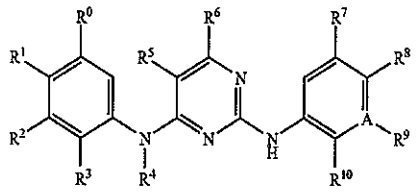
The invention claimed is:

1. A compound of formula I



(I)

each of $R^0$ or $R^2$ independently is hydrogen, $C_1$-$C_8$alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, $C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, or halogen;

$R^1$ is hydrogen, $C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, $C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted Heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, halogen;

$R^3$ is $C_1$-$C_8$alkylsulfinyl, $C_1$-$C_8$alkylsulfonyl, $C_5$-$C_{10}$ arylsulfonyl, or unsubstituted or substituted carbamoyl;

$R^4$ is hydrogen;

$R^5$ is chloro or bromo;

$R^6$ is hydrogen;

each of $R^7$ and $R^9$ independently is hydrogen, $C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, unsubstituted or substituted $C_5$-$C_{10}$aryl, unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S, $C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyloxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, halogen, unsubstituted or substituted carbamoyl, or unsubstituted or substituted sulfamoyl;

$R^8$ is $C_5$-$C_{10}$aryl; unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S; $C_5$-$C_{10}$aryloxy; unsubstituted or substituted heterocyclyloxy; or unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy; and

$R^{10}$ is $C_1$-$C_8$alkyl, halo$C_1$-$C_8$alkyl, $C_1$-$C_8$alkoxy, unsubstituted or substituted heterocyclyl$C_1$-$C_8$alkoxy, unsubstituted or substituted amino, or halogen; and

A is C;

or salts thereof.

2. The compound of claim 1, wherein each of $R^0$, $R^1$ or $R^2$ is hydrogen.

3. The compound of claim 1, wherein $R^3$ is $C_1$-$C_8$alkylsulfonyl, $C_5$-$C_{10}$arylsulfonyl or unsubstituted or substituted carbamoyl.

4. The compound of claim 1, wherein $R^3$ is $C_1$-$C_8$alkylsulfonyl.

5. The compound of claim 1, wherein $R^3$ is $C_5$-$C_{10}$arylsulfonyl.

6. The compound of claim 1, wherein $R^3$ is unsubstituted or substituted carbamoyl.

7. The compound of claim 1, wherein $R^8$ is piperidino, piperazino, N-methylpiperazino, morpholino, phenoxy,

1-methyl-4-piperidyloxy, 3-morpholinopropoxy, 2-morpholinoethoxy or 3-(N-methylpiperazino)-propoxy.

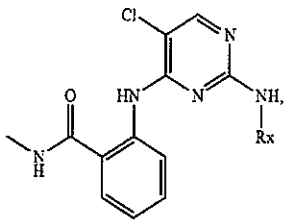
**8**. The compound of claim **1**, wherein $R^8$ is unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S.

**9**. The compound of claim **1**, wherein $R^0$, $R^1$ or $R^2$ is hydrogen; $R^3$ is $C_1$-$C_8$alkylsulfonyl; and $R^8$ is unsubstituted or substituted 5 or 6 membered heterocyclyl comprising 1 or 2 hetero atoms selected from N, O and S.

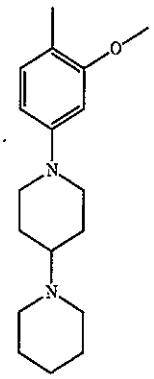
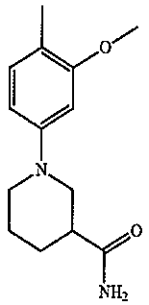
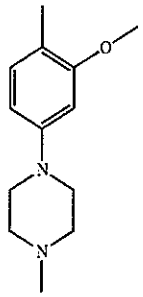
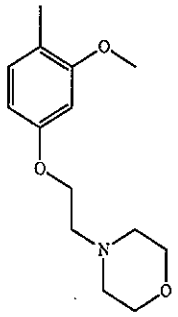
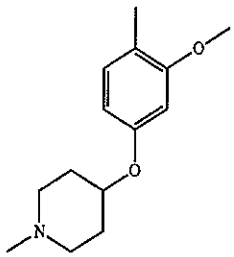
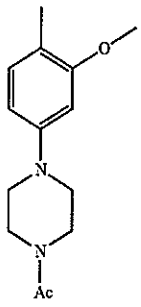
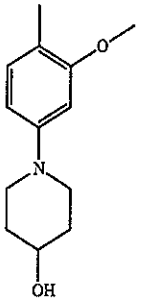
**10**. The compound of claim **9**, wherein $R^8$ is piperidino, piperazino, N-methylpiperazino or morpholino.

**11**. The compound of claim **1**, wherein said compound is selected from the group of compounds with the following names or formulae: 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide;

a compound of the formula



wherein Rx has one of the meanings given in the following table:

| Compound No. | Rx |
|---|---|
| 7-1 |  |
| 7-2 |  |
| 7-3 |  |
| 7-4 |  |
| 7-5 |  |
| 7-7 |  |
| 7-8 |  |

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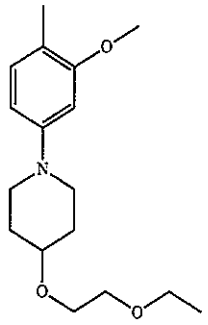
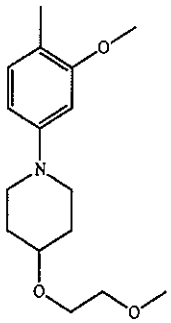
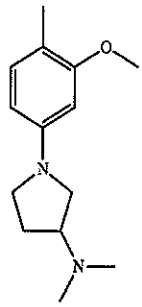
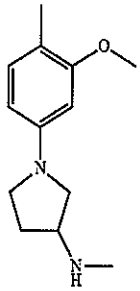
| Compound No. | Rx |
|---|---|
| 7-9 |  |
| 7-10 |  |
| 7-11 |  |
| 7-12 |  |

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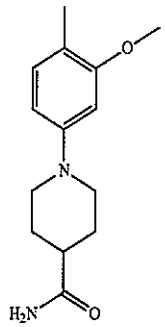
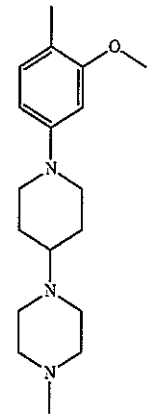
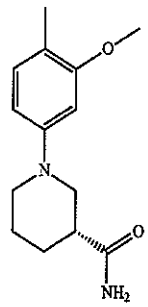
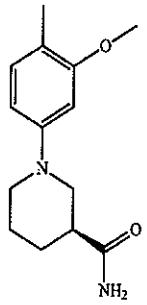
| Compound No. | Rx |
|---|---|
| 7-13 |  |
| 7-14 |  |
| 7-17 |  |
| 7-18 |  |

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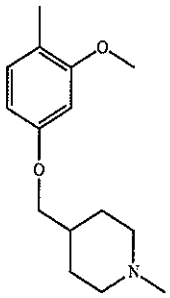
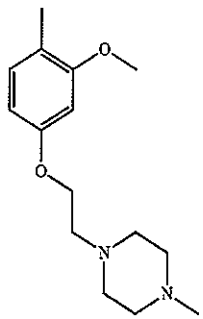
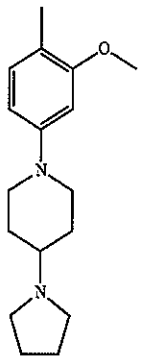
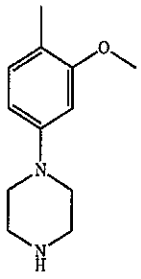
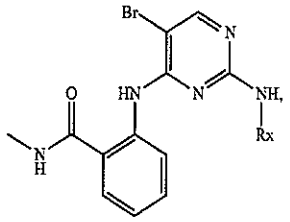
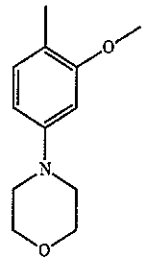
| Compound No. | Rx |
|---|---|
| 7-20 |  |
| 7-21 |  |
| 7-25 |  |
| 7-26 |  |

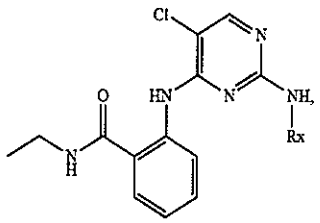
a compound of the formula



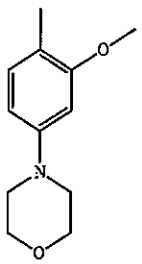
wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 8-2 |  |

a compound of the formula



wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 9-1 |  |

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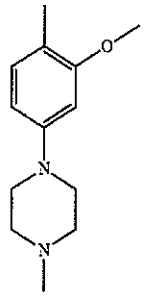
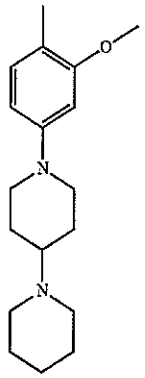
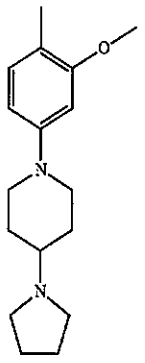
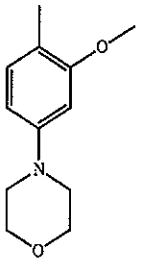
| Compound | Rx |
|---|---|
| 9-2 |  |
| 9-3 |  |
| 9-4 |  |
| 9-5 |  |

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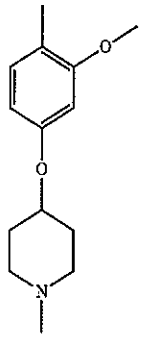
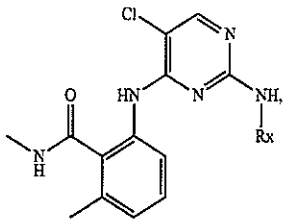
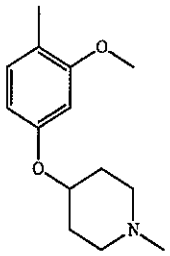
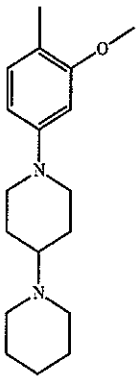
| Compound | Rx |
|---|---|
| 9-6 |  |

a compound of the formula



wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 10-1 |  |
| 10-2 |  |

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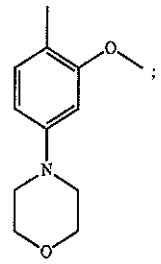
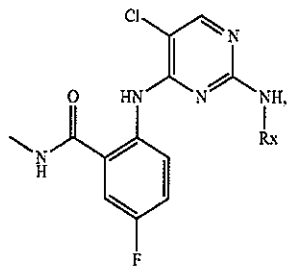
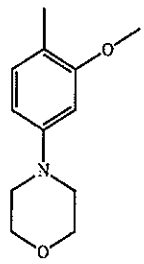
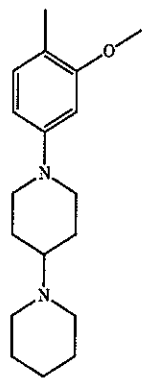
| Compound | Rx |
|---|---|
| 10-3 |  |

a compound of the formula



wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 11-1 |  |
| 11-2 |  |

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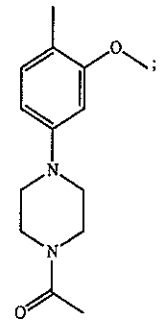
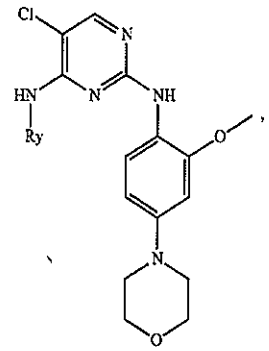
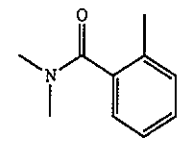
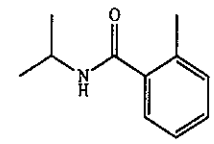
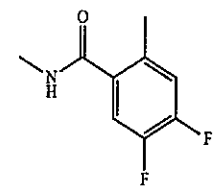
| Compound | Rx |
|---|---|
| 11-4 |  |

a compound of the formula



wherein Ry has one of the meanings given in the following table:

| Compound | R |
|---|---|
| 14-1 |  |
| 14-2 |  |
| 14-3 |  |

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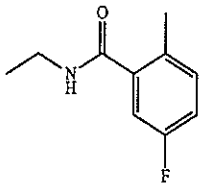
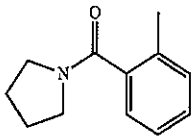
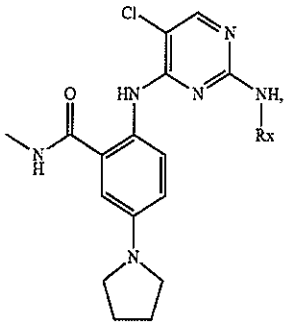
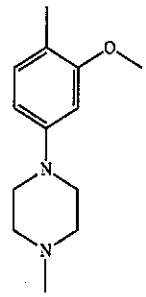
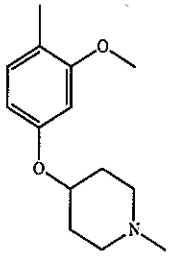
| Compound | R |
|---|---|
| 14-5 |  |
| 14-6 |  |

a compound of the formula



wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 15-1 |  |
| 15-2 |  |

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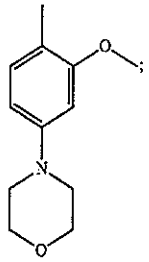
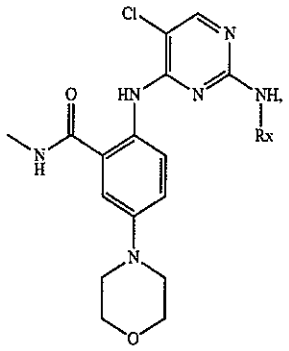
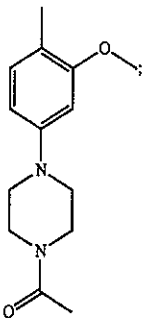
| Compound | Rx |
|---|---|
| 15-3 |  |

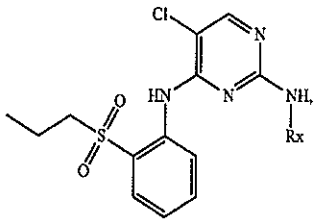
a compound of the formula



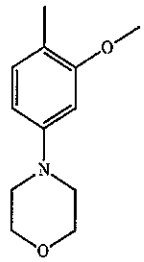
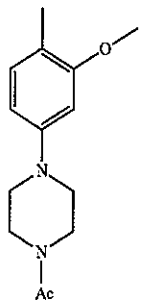
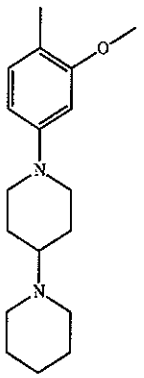
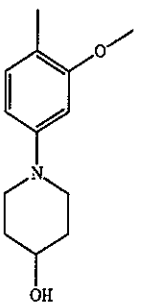
wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 18-1 |  |

a compound of the formula



wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 26-1 |  |
| 26-2 |  |
| 26-3 |  |
| 26-4 |  |

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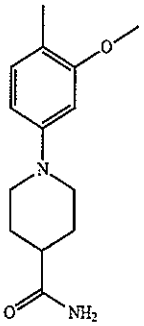
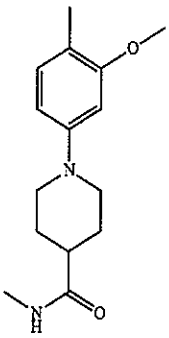
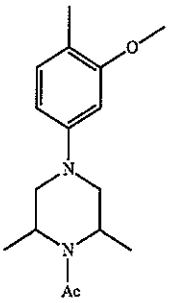
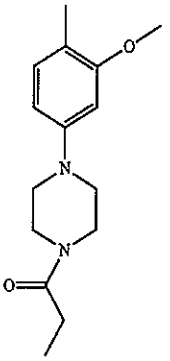
| Compound | Rx |
|---|---|
| 26-5 |  |
| 26-6 |  |
| 26-7 |  |
| 26-8 |  |

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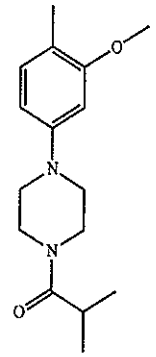
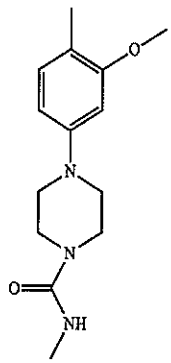
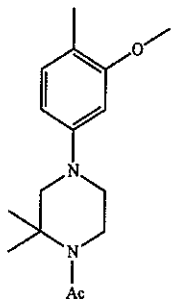
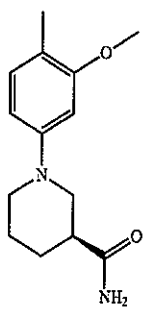
| Compound | Rx |
|---|---|
| 26-9 |  |
| 26-10 |  |
| 26-11 |  |
| 26-12 |  |

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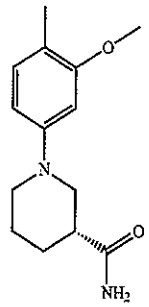
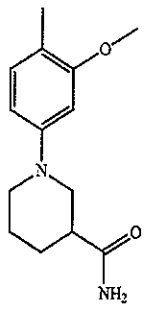
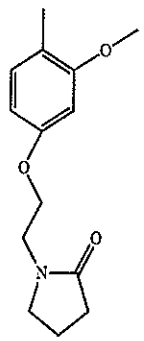
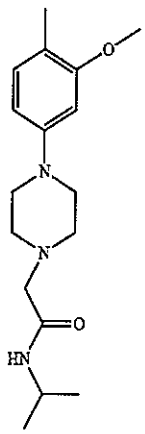
| Compound | Rx |
|---|---|
| 26-13 |  |
| 26-14 |  |
| 26-18 |  |
| 26-21 |  |

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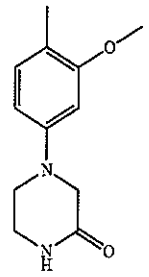
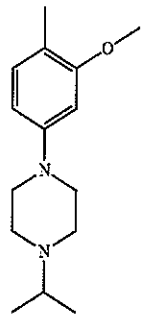
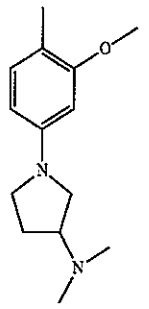
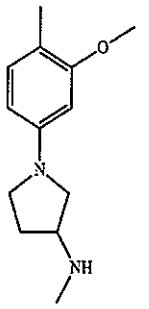
| Compound | Rx |
|---|---|
| 26-22 |  |
| 26-23 |  |
| 26-24 |  |
| 26-25 |  |

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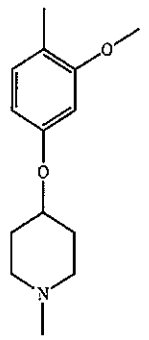
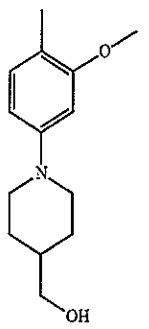
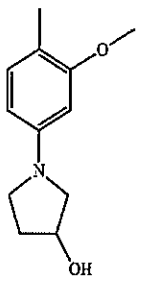
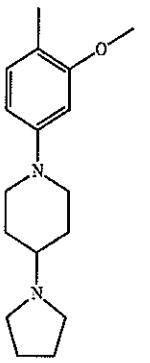
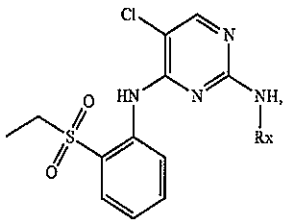
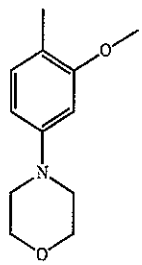
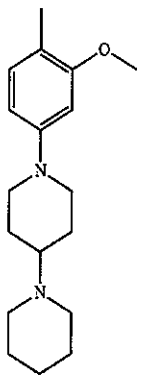
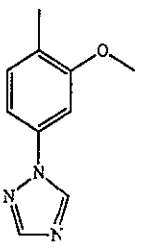
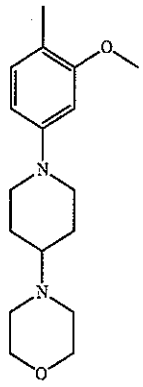
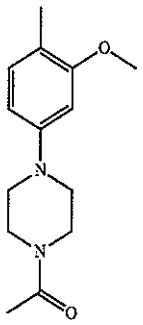
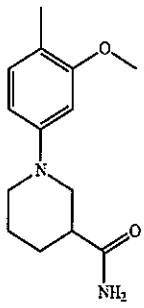
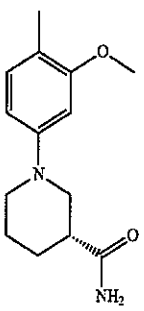
| Compound | Rx |
|---|---|
| 26-26 |  |
| 26-27 |  |
| 26-28 |  |
| 26-29 |  |

a compound of the formula



wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 27-1 |  |
| 27-2 |  |
| 27-3 |  |
| 27-4 |  |
| 27-5 |  |
| 27-6 |  |
| 27-8 |  |

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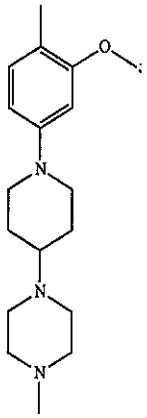
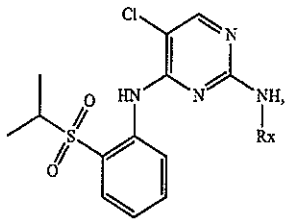
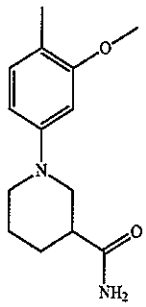
| Compound | Rx |
|---|---|
| 27-9 |  |

a compound of the formula



wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 28-1 |  |

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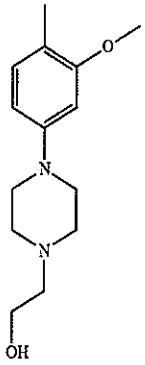
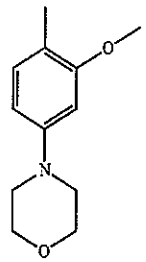
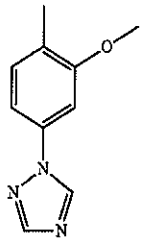
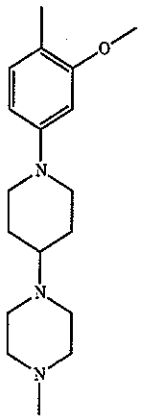
| Compound | Rx |
|---|---|
| 28-2 |  |
| 28-3 |  |
| 28-4 |  |
| 28-5 |  |

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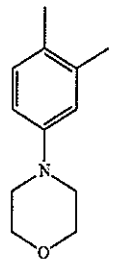
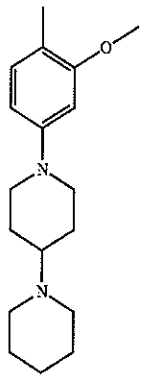
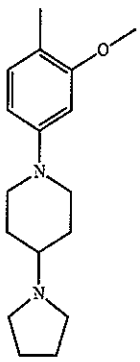
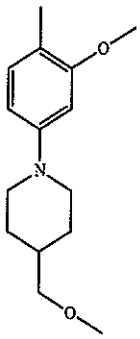
| Compound | Rx |
|---|---|
| 28-6 |  |
| 28-8 |  |
| 28-9 |  |
| 28-10 |  |

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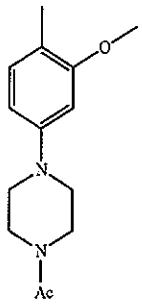
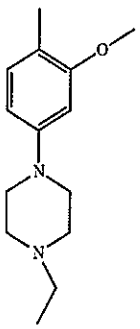
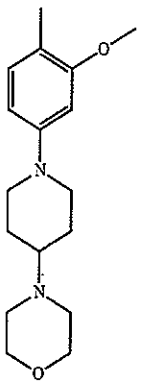
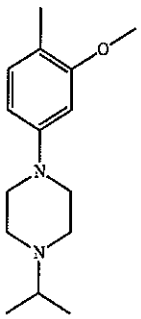
| Compound | Rx |
|---|---|
| 28-11 |  |
| 28-12 |  |
| 28-13 |  |
| 28-14 |  |

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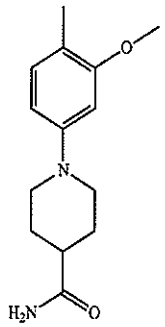
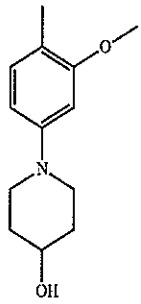
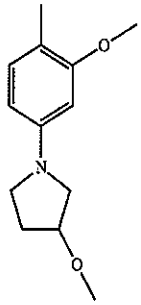
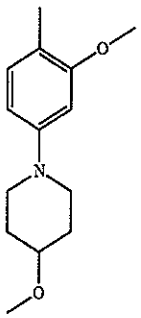
| Compound | Rx |
|---|---|
| 28-15 |  |
| 28-16 |  |
| 28-17 |  |
| 28-18 |  |

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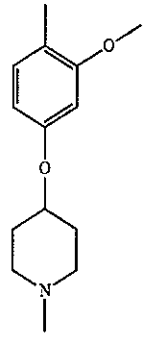
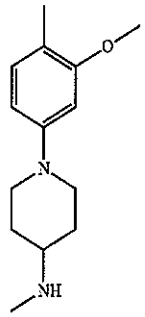
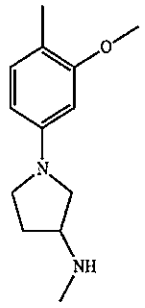
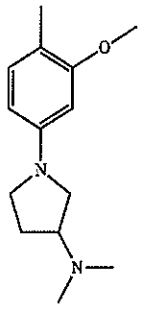
| Compound | Rx |
|---|---|
| 28-19 |  |
| 28-20 |  |
| 28-21 |  |
| 28-22 |  |

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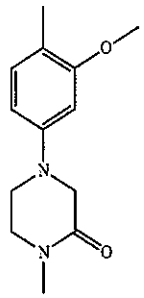
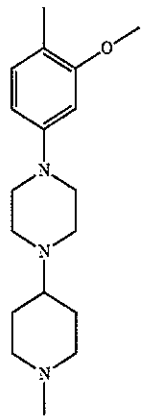
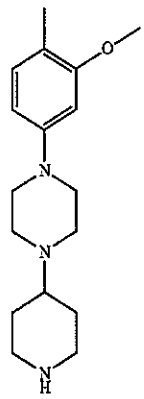
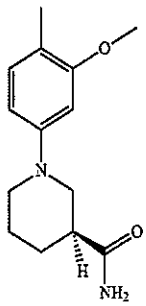
| Compound | Rx |
|---|---|
| 28-23 |  |
| 28-24 |  |
| 28-25 |  |
| 28-27 |  |

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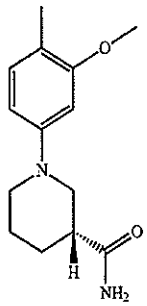
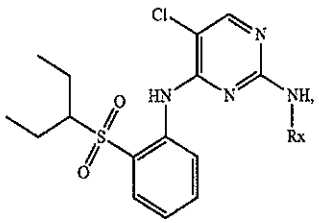
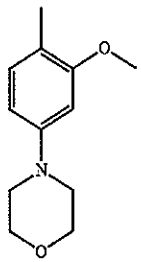
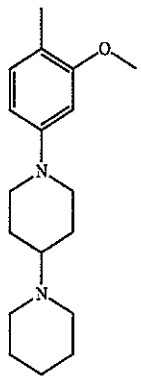
| Compound | Rx |
|---|---|
| 28-28 |  |

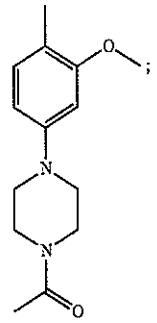
a compound of the formula



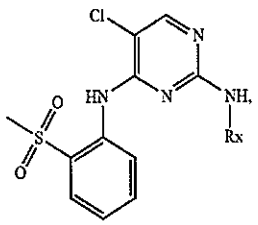
wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 29-1 |  |
| 29-2 |  |

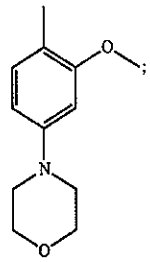
-continued

| Compound | Rx |
|---|---|
| 29-3 |  |

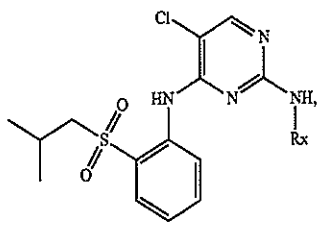
a compound of the formula



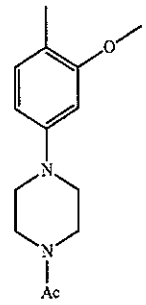
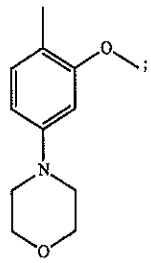
wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 31-2 |  |

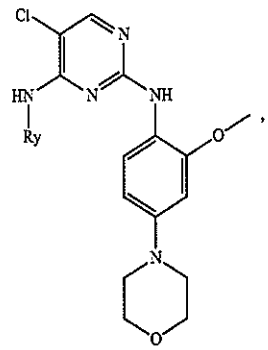
a compound of the formula



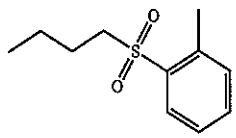
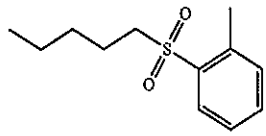
wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 32-1 |  |
| 32-2 |  |

a compound of the formula



wherein Ry has one of the meanings given in the following table:

| Compound | Ry |
|---|---|
| 34-1 |  |
| 34-3 |  |

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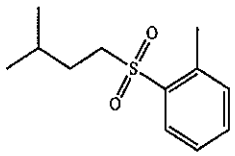
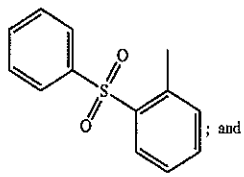
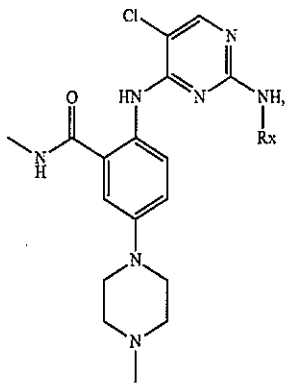
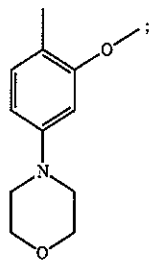
| Compound | Ry |
|---|---|
| 34-4 |  |
| 34-6 |  ; and |

a compound of the formula



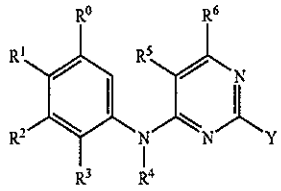
wherein Rx has one of the meanings given in the following table:

| Compound | Rx |
|---|---|
| 35-1 |  ; |

or a pharmaceutically acceptable salt thereof.

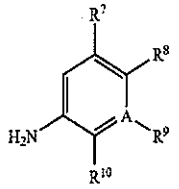
12. The compound of claim 1, wherein said compound is 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl -phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide, or $N^2$-(4-[1,4']Bipiperidinyl-1'-yl-2-methoxy-phenyl)-5-chloro-$N^4$-[2-(propane-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

13. A process for the production of a compound of formula I according to claim 1, comprising reacting a compound of formula II



(II)

wherein $R^0$, $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, and $R^6$ are as defined in claim 1, and Y is a leaving group, with a compound of formula III



(III)

wherein A, $R^7$, $R^8$, $R^9$ and $R^{10}$ are as defined in claim 1;

and, if desired, converting a compound of formula I, wherein the substituents have the meaning as defined in claim 1, into another compound of formula I as defined in claim 1;

and recovering the resulting compound of formula I in free from or as a salt, and, when required, converting the compound of formula I obtained in free form into the desired salt, or an obtained salt into the free form.

14. A pharmaceutical composition comprising a compound according to claim 1, as active ingredient together with one or more pharmaceutically acceptable diluents or carriers.

15. A combination comprising a therapeutically effective amount of a compound according to claim 1 and one or more known drug substances, said further drug substance being useful in the treatment of neoplastic diseases or immune system disorders.

16. A method for the treatment of breast tumors in a subject in need thereof which comprises administering an effective amount of a compound according to claim 1 or a pharmaceutical composition comprising same.

17. The method of claim 16, wherein said compound is 2-[5-chloro-2-(2-methoxy-4-morpholin-4-yl -phenylamino)-pyrimidin-4-ylamino]-N-methyl-benzamide, or $N^2$-(4-[1,4']Bipiperidinyl-1'-yl-2-methoxy-phenyl)-5-chloro-$N^4$-[2-(propane-1-sulfonyl)-phenyl]-pyrimidine-2,4-diamine, or a pharmaceutically acceptable salt thereof.

* * * * *

# APPENDIX E

NOVARTIS
ONCOLOGY

**Chandrika Kumar, Ph.D.**
Associate Director
Drug Regulatory Affairs
Oncology Global Development

**Novartis Pharmaceuticals Corporation**
One Health Plaza, Bldg 104
East Hanover, NJ 07936-1080
Tel: 862-778-5933
Fax: 973-781-5217
Email: chandrika.kumar@novartis.com

Robert Justice, MD
Director
Division of Oncology Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

**IND 109,272**
**LDK378**

**INVESTIGATIONAL NEW DRUG APPLICATION**

**Serial No. 0000**

Dear Dr. Justice:

In accordance with 21 CFR §312.23, Novartis Pharmaceuticals Corporation is hereby submitting an Investigational New Drug Application (IND) for the following:

**Drug Product: LDK378 (oral)**
**Indication: Treatment of tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK)**

LDK378 is an orally bioavailable small molecule inhibitor of the anaplastic lymphoma kinase (ALK). Genetic aberrations in ALK result in ligand-independent constitutive activation of the ALK kinase activity and lead to the genesis of several cancers such as anaplastic large-cell non-Hodgkin's lymphoma (ALCL), non-small cell lung cancer (NSCLC), inflammatory myofibroblastic tumors, breast cancer, and neuroblastoma. In ALCL, the ALK kinase domain is fused to the nucleophosmin gene (NPM) through a chromosomal translocation creating the NPM-ALK fusion gene. In NSCLC, the ALK kinase domain is fused to the echinoderm microtubule-associated protein-like 4 (EML4) creating the EML4-ALK fusion gene.

LDK378 is a potent and selective ATP-competitive inhibitor of ALK kinase activity. LDK378 inhibits the *in vitro* proliferation of multiple ALK-dependent patient-derived cell lines such as: Karpas299, an ALCL human cell line that expresses the constitutively active NPM-ALK fusion protein; H2228, a NSCLC human cell line that expresses the constitutively active EML4-ALK fusion protein; and NB-1, a human neuroblastoma cell line that has an amplification of the full length ALK gene. LDK378 is also a potent inhibitor of *in vivo* tumor growth in mouse and rat models of both ALCL and NSCLC, inducing >70% regression at well tolerated doses.

Thus, based on the emerging clinical data for Alk inhibitors and the available preclinical data for LDK378, it is anticipated that LDK378 may be effective in the treatment of patients with tumors characterized by genetic abnormalities in ALK. Accordingly, Novartis believes that there is sufficient preclinical safety and potential efficacy data to move forward with an IND submission.

Provided in this IND application is a summary of the relevant safety data and CMC information to support the initiation of the following protocol:

**CLDK378X2101:** The proposed initial study is a phase I, multicenter, open-label dose escalation study of LDK378, administered orally in adult patients with tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK). The study will investigate the safety, PK, PD and preliminary efficacy of LDK378. There will be two phases in the study, an escalation phase and an expansion phase. The escalation phase will include a PK-run-in period followed by the treatment period in which LDK378 will be given in a continuous daily dosing. The expansion phase will start after the MTD has been estimated in order to identify patient populations who could potentially benefit from LDK378 treatment. There will be 3 arms in the expansion phase, which include:

- ALK-translocated patients with NSCLC who have progressed following treatment with an ALK inhibitor,
- ALK-translocated patients with NSCLC not previously treated with an ALK inhibitor,
- ALK-translocated patients with tumor types other than NSCLC

In line with the FDA's Critical Path Initiative to expand the use of Bayesian models in drug development, an adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used to estimate the MTD during the dose escalation part of the study.

Novartis Pharmaceuticals Corporation considers the information contained within this IND and all subsequent amendments and annual reports to be confidential, and their contents are not to be disclosed without written consent.

The relevant technical details of this electronic submission are as follows:

Submission size: Approximately 70 MB
Electronic Media: Sent through the Electronic Submissions FDA Gateway
Virus Scan: VirusScan Enterprise + AntiSpyware Enterprise 8.5.0i
The submission is virus free.

If you have any questions or comments, please contact me at (862)778-5933.

Sincerely,

Chandrika Kumar Ph.D.
Associate Director
Drug Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

# INVESTIGATIONAL NEW DRUG APPLICATION (IND)

*(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*

*Form Approved:* OMB No. 0910-0014.
*Expiration Date: May 31, 2009*
*See OMB Statement on Reverse.*

**NOTE:** No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
Novartis Pharmaceuticals Corporation

2. DATE OF SUBMISSION
10/08/2010

3. ADDRESS *(Number, Street, City, State and Zip Code)*
One Health Plaza
East Hanover, NJ 07936-1080

4. TELEPHONE NUMBER *(Include Area Code)*
862-778-5933

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
LDK378

6. IND NUMBER *(If previously assigned)*
109272

7. INDICATION(S) *(Covered by this submission)*
Treatment of tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK)

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED:
☑ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR Part 314.420)*, AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION.

10. ***IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.***

SERIAL NUMBER: 0

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

☑ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY/MICROBIOLOGY
☐ PHARMACOLOGY/TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION
☐ ANNUAL REPORT
☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED
☐ OTHER _____ *(Specify)*

**CHECK ONLY IF APPLICABLE**

**JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.**

☐ TREATMENT IND 21 CFR 312.35(d) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

**FOR FDA USE ONLY**

| CDR/DBIND/DGD RECEIPT STAMP | DDR RECEIPT STAMP | DIVISION ASSIGNMENT: |
|---|---|---|
| | | IND NUMBER ASSIGNED: |

12. **CONTENTS OF APPLICATION**

This application contains the following items: *(Check all that apply)*

- [x] 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- [x] 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- [x] 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- [x] 4. General Investigational plan *[21 CFR 312.23(a)(3)]*
- [x] 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- [x] 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - [x] a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - [x] b. Investigator data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [x] c. Facilities data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - [x] d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- [x] 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - [x] Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- [x] 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- [ ] 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- [ ] 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? [x] YES [ ] NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? [x] YES [ ] NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Matthew Robson MD

Oncology Senior Director/Clinical Research Physician

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Dionigi Maladorno MD
Senior Brand Safety Leader
Integrated Medial Safety

**I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set fourth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.**

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Chandrika Kumar, Associate Director,
Drug Regulatory Affairs

17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE

Kumar Chandrika

Digitally signed by Kumar Chandrika
DN: cn=Kumar Chandrika, ou=people, PH, serialNumber=565272, dc=com, novartis
Reason: I am the author of this document
Date: 2010.10.02 23:47:43 -04'00'

18. ADDRESS *(Number, Street, City, State and Zip Code)*

One Health Plaza
East Hanover, NJ 07936-1080

19. TELEPHONE NUMBER *(Include Area Code)*

862-778-5933

20. DATE

10/08/2010

**(WARNING:** A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

**Please DO NOT RETURN this application to this address.**

# APPENDIX F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205755

**NDA ACKNOWLEDGMENT**

Novartis Pharmaceuticals Corporation
Attention: Yanina Gutman, Pharm.D.
Senior Associate Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936

Dear Dr. Gutman:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Ceralk (ceritinib) capsules, 150 mg

Date of Application: December 24, 2013

Date of Receipt: December 24, 2013

Our Reference Number: NDA 205755

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 22, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-7032.

Sincerely,

*{See appended electronic signature page}*

Karen Boyd, M.S.
Senior Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

KAREN C BOYD
01/06/2014

# APPENDIX G

US Regulatory Record Indexing Report for INDs

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 4/24/2014 | 20140424 0357 Request for FDA Mtg Type B | Request for Type B meeting to discuss the design of a Phase II study which will evaulate the efficacy and safety of ceritinib in patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLS) with metastases to the brain and/or leptomeninges. (eCTD-seq0357) | Request for FDA Mtg | 0357 |
| IND 109272 | LDK378 | 4/23/2014 | 20140423 0353 New Investigator CLDK378A2303,C | New investigators, studies CLDK378A2108 and CLDK378A2303. (eCTD-seq0353) | New Investigator | 0353 |
| IND 109272 | LDK378 | 4/16/2014 | 20140416 0350 Response to FDA Request 20140408 Email | Response to FDA email request dated April 8, 2014 regarding the number of patients enrolled on the expanded access program for IND 109272. (eCTD-seq0350) | Response to FDA Request | 0350 |
| IND 109272 | LDK378 | 4/16/2014 | 20140416 0355 Letter of Authorization | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use study to be filed by the Ravi Salgia, MD. (eCTD-seq0355) | Letter of Authorization | 0355 |
| IND 109272 | LDK378 | 4/15/2014 | 20140415 0354 Safety Report PHHY2014AT1481 | PHHY2014AT148151 (eCTD-seq0354) | Safety Report | 0354 |
| IND 109272 | LDK378 | 4/11/2014 | 20140411 0352 Letter of Authorization | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use study to be filed by Susan Cohn, MD. (eCTD-seq0352) | Letter of Authorization | 0352 |
| IND 109272 | LDK378 | 4/8/2014 | 20140408 Email FDA Clinical Information Request | Email request from FDA regarding the number of patients enrolled on the expanded access program for IND 109272. | Email | |
| IND 109272 | LDK378 | 4/7/2014 | 20140407 0347 Safety Report PHHO2014KR003 Follow-Up | PHHO2014KR003474; follow-up (eCTD-seq0347) | Safety Report | 0347 |
| IND 109272 | LDK378 | 4/4/2014 | 20140404 0346 Safety Report PHHY2013NL111( Follow-up | PHHY2013NL111601; follow-up (eCTD-seq0346). | Safety Report | 0346 |
| IND 109272 | LDK378 | 4/2/2014 | 20140320 0333 Safety Report PHHO2013KR008 Follow-up | PHHO2013KR008191; follow-up (eCTD-seq0333). | Safety Report | 0333 |
| IND 109272 | LDK378 | 4/2/2014 | 20140402 0341 New Investigator CLDK378A2303,C | New Investigators for Protocol CLDK378A2303 and CLDK378A2402. (eCTD-seq0341) | New Investigator | 0341 |
| IND 109272 | LDK378 | 3/31/2014 | 20140331 0343 Safety Report PHHY2014HK019 Follow-up | PHHY2014HK019244 Follow-up (eCTD-seq0343) | Safety Report | 0343 |
| IND 109272 | LDK378 | 3/28/2014 | 20140328 0342 Safety Report PHHO2014IT0043 7-day | PHHO2014IT004390 7-day (eCTD-seq0342) | Safety Report | 0342 |
| IND 109272 | LDK378 | 3/21/2014 | 20140321 0335 Safety Report PHHO2013TW016 | PHHO2013TW016939; follow-up (eCTD-seq0335) | Safety Report | 0335 |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
|---|---|---|---|---|---|---|
| | | | Follow-Up | | | |
| IND 109272 | LDK378 | 3/20/2014 | 20140320 0334 Safety Report PHHO2013KR008( Follow-up | PHHO2013KR008644; follow-up (eCTD-seq0334). | Safety Report | 0334 |
| IND 109272 | LDK378 | 3/20/2014 | 20140320 0332 Safety Report PHHO2014KR002 Follow-up | PHHO2014KR002139; follow-up (eCTD-seq0332). | Safety Report | 0332 |
| IND 109272 | LDK378 | 3/19/2014 | 20140319 0331 Safety Report PHHY2014NL014 Follow-up | PHHY2014NL014300; follow-up (eCTD-seq0331). | Safety Report | 0331 |
| IND 109272 | LDK378 | 3/18/2014 | 20140318 0329 Safety Report PHHO2014ES001 Follow-up | PHHO2014ES001883; follow-up (eCTD-Seq0329) | Safety Report | 0329 |
| IND 109272 | LDK378 | 3/17/2014 | 20140317 0327 Change in Protocol CLDK378A2402 Amendment 2 | Amendment 2 to Protocol CLDK378A2402. (eCTD-seq0327) | Change in Protocol | 0327 |
| IND 109272 | LDK378 | 3/14/2014 | 20140314 0328 Safety Report PHHY2014FR003( | PHHY2014FR003015(eCTD-seq0328) | Safety Report | 0328 |
| IND 109272 | LDK378 | 3/12/2014 | 20140312 0322 Letter of Authorization | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use study to be filed by J. Thaddeus Beck, MD. (eCTD-seq0322) | Letter of Authorization | 0322 |
| IND 109272 | LDK378 | 3/12/2014 | 20140312 0326 Safety Report PHHY2014FR016 Follow-up | PHHY2014FR016443 Follow-up (eCTD-seq0326) | Safety Report | 0326 |
| IND 109272 | LDK378 | 3/11/2014 | 20140311 0323 New Investigator CLDK378A2303,C | New Investigators for Protocols CLDK378A2303 and CLDK378A2402. (eCTD-seq0323) | New Investigator | 0323 |
| IND 109272 | LDK378 | 3/10/2014 | 20140310 0324 Safety Report PHHO2013KR000 Follow-up | PHHO2013KR000927 follow-up (eCTD-seq0324) | Safety Report | 0324 |
| IND 109272 | LDK378 | 3/10/2014 | 20140310 0325 Safety Report PHHO2014JP002 Follow-up | PHHO2014JP002851 follow-up (eCTD-seq0325) | Safety Report | 0325 |
| IND 109272 | LDK378 | 3/7/2014 | 20140307 0315 Change in Regulatory Contact | Submission of change in regulatory contact from Denisa Weinstein to Angela M. Neufeld. (eCTD-seq0315) | General Correspondence | 0315 |
| IND 109272 | LDK378 | 3/7/2014 | 20140307 Safety Report PHHY2014FR003( 7-Day | PHHY2014FR003015 7-Day Safety Report (PS) | Safety Report | |
| IND 109272 | LDK378 | 3/6/2014 | 20140306 0320 Safety Report PHHO2014ES001 Follow-up | PHHO2014ES001883 (eCTD-seq0320) | Safety Report | 0320 |
| IND 109272 | LDK378 | 3/5/2014 | 20140305 0317 Letter of Authorization | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use study to be filed by Tarek Mekhail, MD. | Letter of Authorization | 0317 |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
|---|---|---|---|---|---|---|
| | | | | (eCTD-seq0317) | | |
| IND 109272 | LDK378 | 3/5/2014 | 20140305 0319 Safety Report PHHO2014US002 Follow-Up | PHHO2014US002127 Follow-Up (eCTD-seq0319) | Safety Report | 0319 |
| IND 109272 | LDK378 | 3/5/2014 | 20140305 0318 Safety Report PHHO2014JP002 | PHHO2014JP002851 (eCTD-seq0318) | Safety Report | 0318 |
| IND 109272 | LDK378 | 3/5/2014 | 20140305 0321 Safety Report PHHO2013IT0114 | PHHO2013IT011464 follow-up (eCTD-seq0321) | Safety Report | 0321 |
| IND 109272 | LDK378 | 3/3/2014 | 20140303 0316 Safety Report PHHY2014HK019 | PHHY2014HK019244 (eCTD-seq0316) | Safety Report | 0316 |
| IND 109272 | LDK378 | 2/25/2014 | 20140225 0314 Safety Report PHHO2014ES001 | PHHO2014ES001883 (eCTD-seq0314) | Safety Report | 0314 |
| IND 109272 | LDK378 | 2/25/2014 | 20140225 Safety Report PHHO2014US002 7-Day | PHHO2014US002127 7-Day Safety Report (PS) | Safety Report | |
| IND 109272 | LDK378 | 2/24/2014 | 20140224 0312 Safety Report PHHO2013JP014 Follow-up | PHHO2013JP014373; follow-up (eCTD-seq0312) | Safety Report | 0312 |
| IND 109272 | LDK378 | 2/24/2014 | 20140224 0313 Safety Report PHHY2014FR016 Follow-up | PHHY2014FR016443 (eCTD-seq0313) | Safety Report | 0313 |
| IND 109272 | LDK378 | 2/20/2014 | 20140220 0309 New Investigator A2303,A2402,A21 | New Investigator for Protocols CLDK378A2303 and CLDK378A2402 and CLDK378A2110. | New Investigator | 0309 |
| IND 109272 | LDK378 | 2/20/2014 | 20140220 0311 Safety Report PHHO2014US002 | PHHO2014US002127 (eCTD-seq0311) | Safety Report | 0311 |
| IND 109272 | LDK378 | 2/17/2014 | 20140217 0307 Safety Report PHHY2014CA014 | PHHY2014CA014187 (eCTD-seq0307) | Safety Report | 0307 |
| IND 109272 | LDK378 | 2/17/2014 | 20140217 0308 Safety Report PHHY2014NL014 | PHHY2014NL014300 (eCTD-seq0308) | Safety Report | 0308 |
| IND 109272 | LDK378 | 2/17/2014 | 20140217 Safety Report PHHY2014FR916 7-Day | PHHY2014FR916443; safety report 7-Day (PS) | Safety Report | |
| IND 109272 | LDK378 | 2/14/2014 | 20140214 0304 Change in Protocol CLDK378A2108 Amendment 1 | Amendment 1 to Protocol CLDK378A2108. (eCTD-seq0304) | Change in Protocol | 0304 |
| IND 109272 | LDK378 | 2/14/2014 | 20140214 0306 Safety Report PHHO2013US009 Follow-up | PHHO2013US009607; follow-up (eCTD-seq0306) | Safety Report | 0306 |
| IND 109272 | LDK378 | 2/12/2014 | 20140212 Safety Report PHHO2014KR002 7-Day | PHHO2014KR002139 7-Day safety report (PS) | Safety Report | |
| IND 109272 | LDK378 | 2/11/2014 | 20140211 0305 Letter of | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use | Letter of | 0305 |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
|---|---|---|---|---|---|---|
| | | | Authorization | study to be filed by Taofeek Owonikoko, MD. (eCTD-seq0305) | Authorization | |
| IND 109272 | LDK378 | 2/10/2014 | 20140210 Safety Report PHHY2014CA014' 7-Day | PHHY2014CA014187; 7-Day Safety Report (PS) | Safety Report | |
| IND 109272 | LDK378 | 2/10/2014 | 20140210 Safety Report PHHY2014NL014: 7-Day | PHHY2014NL014300 7-Day Safety Report (PS) | Safety Report | |
| IND 109272 | LDK378 | 2/7/2014 | 20140207 0303 Letter of Authorization | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use study to be filed by David Gerber, MD. (eCTD-seq0303) | Letter of Authorization | 0303 |
| IND 109272 | LDK378 | 2/6/2014 | 20140206 0302 Safety Report PHHO2013US008 | PHHO2013US008426 follow-up(eCTD-seq0302) | Safety Report | 0302 |
| IND 109272 | LDK378 | 2/5/2014 | 20140205 0295 New Investigator CLDK378A2303,C | New Investigators for Protocols CLDK378A2303, CLDK378A2402 and CLDK378A2110. (eCTD-seq0295) | New Investigator | 0295 |
| IND 109272 | LDK378 | 2/5/2014 | 20140205 0301 Safety Report PHHO2013FR015 Follow-Up | PHHO2013FR015995 Follow-Up (eCTD-seq 0301) | Safety Report | 0301 |
| IND 109272 | LDK378 | 2/4/2014 | 20140204 0299 Safety Report PHHO2013JP007 follow-up | PHHO2013NL014748; follow-up (eCTD-seq0299) | Safety Report | 0299 |
| IND 109272 | LDK378 | 2/4/2014 | 20140204 0300 Safety Report PHHO2013IT0095 follow-up | PHHO2013IT009526; follow-up (eCTD-seq0300) | Safety Report | 0300 |
| IND 109272 | LDK378 | 2/4/2014 | 20140204 0298 Safety Report PHHO2013JP014 Follow-up | PHHO2013JP014373 Follow-up (eCTD-seq0298) | Safety Report | 0298 |
| IND 109272 | LDK378 | 1/29/2014 | 20140129 0297 Withdrawal of Proposed Proprietary Name | Novartis is withdrawing the proposed proprietary name CERALK™ from IND 109272. (eCTD-seq0297) | General Correspondence | 0297 |
| IND 109272 | LDK378 | 1/29/2014 | 20140129 0296 Safety Report PHHO2013US006 Follow-Up | PHHO2013US006452; follow-up (eCTD-seq0296) | Safety Report | 0296 |
| IND 109272 | LDK378 | 1/27/2014 | 20140127 0294 Safety Report PHHY2013US145 Follow-up | PHHY2013US145701; follow-up (eCTD-seq0294) | Safety Report | 0294 |
| IND 109272 | LDK378 | 1/23/2014 | 20140123 0292 Letter of Authorization | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use study to be filed by Abraham Chachoua, MD. (eCTD-seq0292) | Letter of Authorization | 0292 |
| IND 109272 | LDK378 | 1/23/2014 | 20140123 0293 Safety Report PHHO2013IT0114 Follow-up | PHHO2013IT011464; follow-up (eCTD-seq0293) | Safety Report | 0293 |
| IND 109272 | LDK378 | 1/14/2014 | 20140114 0291 Safety Report | PHHO2013US003591 Follow-up (eCTD- | Safety Report | 0291 |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
|---|---|---|---|---|---|---|
| | | | PHHO2013US003! Follow-up | seq0291) | | |
| IND 109272 | LDK378 | 1/13/2014 | 20140113 0290 Safety Report PHHO2013TW016 | PHHO2013TW016939 (eCTD-seq0290) | Safety Report | 0290 |
| IND 109272 | LDK378 | 1/8/2014 | 20140108 0289 New Investigator CLDK378A2303,C | New Investigators for protocols CLDK378A2303 and CLDK378A2402 (eCTD-seq0289) | New Investigator | 0289 |
| IND 109272 | LDK378 | 1/3/2014 | 20140103 0263 DSUR 2012-2013 | Annual report (DSUR) covering the period 2012-2013 (eCTD-seq0263) | DSUR | 0263 |
| IND 109272 | LDK378 | 1/3/2014 | 20140103 Safety Report PHHO2013TW016 7-Day | PHHO2013TW016939; 7-Day Safety Report (PS) | Safety Report | |
| IND 109272 | LDK378 | 1/2/2014 | 20140102 0286 Safety Report PHHO2013US006 Follow-up | PHHO2013US006442 Follow-up (eCTD-seq0286) | Safety Report | 0286 |
| IND 109272 | LDK378 | 1/2/2014 | 20140102 0287 Safety Report PHHO2013US006 Follow-up | PHHO2013US006452 Follow-up (eCTD-seq0287) | Safety Report | 0287 |
| IND 109272 | LDK378 | 12/31/2013 | 20131231 0275 Safety Report PHHO2013US006 Follow-up | PHHO2013US006452; follow-up (eCTD-seq0275) | Safety Report | 0275 |
| IND 109272 | LDK378 | 12/31/2013 | 20131231 0285 Safety Report PHHO2013US006 Follow-up | PHHO2013US006204; Follow-up (eCTD-seq0285) | Safety Report | 0285 |
| IND 109272 | LDK378 | 12/31/2013 | 20131231 0284 Safety Report PHHO2013FR015 Follow-up | PHHO2013FR015995; follow-up (eCTD-seq0284) | Safety Report | 0284 |
| IND 109272 | LDK378 | 12/24/2013 | 20131224 0282 Safety Report PHHO2012JP017 Follow-up | PHHO2012JP017066; follow-up (eCTD-seq0282). | Safety Report | 0282 |
| IND 109272 | LDK378 | 12/23/2013 | 20131223 0277 Response to FDA Request 20131202 Non-hold Comment A2110 | Response to FDA non-hold comment dated December 2, 2013 on the Study CLDK378A2110 protocol. (eCTD-seq0277) | Response to FDA Request | 0277 |
| IND 109272 | LDK378 | 12/23/2013 | 20131223 0274 Safety Report PHHO2013JP010 Follow-up | PHHO2013JP010761 Follow-up (eCTD-seq0274) | Safety Report | 0274 |
| IND 109272 | LDK378 | 12/21/2013 | 20131221 0280 Safety Report PHHO2013US016 | PHHO2013US016078 (eCTD-seq0280). | Safety Report | 0280 |
| IND 109272 | LDK378 | 12/21/2013 | 20131221 0279 Safety Report PHHY2013US145 | PHHY2013US145701 (eCTD-seq0279). | Safety Report | 0279 |
| IND 109272 | LDK378 | 12/21/2013 | 20131221 0281 Safety Report PHHO2013IT0114 Follow-up | PHHO2013IT011464; follow-up (eCTD-seq0281) | Safety Report | 0281 |
| IND 109272 | LDK378 | 12/19/2013 | 20131219 0278 Safety Report PHHO2013FR015 | PHHO2013FR015995 (eCTD-seq0278) | Safety Report | 0278 |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 12/18/2013 | 20131218 0276 Letter of Authorization | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use study to be filed by sponsor Jennifer Tseng, MD. (eCTD-seq0276) | Letter of Authorization | 0276 |
| IND 109272 | LDK378 | 12/17/2013 | 20131217 0273 Letter of Authorization | Novartis authorizes the FDA to cross-reference Novartis IND 109,272 for ceritinib (LDK378) in support of a compassionate use study to be filed by sponsors Jeffrey L. Berenberg, MD, Alice Shaw, MD and Aaron Mansfield, MD. (eCTD-seq0273) | Letter of Authorization | 0273 |
| IND 109272 | LDK378 | 12/17/2013 | 20131217 0272 Safety Report PHHO2013TW013 Follow-up | PHHO2013TW013119 Follow-up (eCTD-seq0272) The receipts are not available for this submission. | Safety Report | 0272 |
| IND 109272 | LDK378 | 12/16/2013 | 20131216 0268 New Investigator CLDK378A2303 | New Investigator for Study CLDK378A2303. (eCTD-seq0268) | New Investigator | 0268 |
| IND 109272 | LDK378 | 12/12/2013 | 20131212 0267 General Correspondence iPSP | Submission provides a follow-up to FDA correspondence regarding initial Pediatric Study Plan (iPSP). (eCTD-seq0267) | General Correspondence | 0267 |
| IND 109272 | LDK378 | 12/12/2013 | 20131212 0271 Safety Report PHHO2013FR014 Follow-up | PHHO2013FR014990; follow-up (eCTDseq0271) | Safety Report | 0271 |
| IND 109272 | LDK378 | 12/12/2013 | 20131212 0270 Safety Report PHHO2013FR014 Follow-up | PHHO2013FR014506; follow-up (eCTDseq0270) | Safety Report | 0270 |
| IND 109272 | LDK378 | 12/12/2013 | 20131212 0269 Safety Report PHHO2013JP014 Follow-up | PHHO2013JP014592; follow-up (eCTDseq0269) | Safety Report | 0269 |
| IND 109272 | LDK378 | 12/9/2013 | 20131209 0265 New Investigator CLDK378A2402, A2303 | New Investigators for Protocol(s) CLDK378A2402, A2303, (eCTD-seq0265) | New Investigator | 0265 |
| IND 109272 | LDK378 | 12/6/2013 | 20131206 0262 Clinical Information Amendment IB Edition 6 | Submission provides Edition 6 of the LDK378 Investigator's Brochure (dated 27-Nov-2013). (eCTD-seq0262) | Clinical Information Amendment | 0262 |
| IND 109272 | LDK378 | 12/5/2013 | 20131205 0264 Safety Report PHHO2013DE013 Follow-up | PHHO2013DE013754 Follow-up (eCTD-seq0264) | Safety Report | 0264 |
| IND 109272 | LDK378 | 12/4/2013 | 20131204 0266 Safety Report PHHO2013KR014 | PHHO2013KR014602 (eCTD-Seq0266) | Safety Report | 0266 |
| IND 109272 | LDK378 | 12/2/2013 | 20131202 0254 New Investigator CLDK378A2402 and CLDK378A2303 | CLDK378A2402 and CLDK378A2303; eCTDseq0254 | New Investigator | 0254 |
| IND 109272 | LDK378 | 12/2/2013 | 20131202 Advice-Information Request A2110 | FDA request regarding clinical protocol CLDK378A2110. | Advice-Information Request | |
| | | | 20131107 0248 | | | |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 11/28/2013 | Safety Report PHHO2013IT0114 Follow-up | PHHO2013IT011464; follow-up (eCTD-seq0248) | Safety Report | 0248 |
| IND 109272 | LDK378 | 11/27/2013 | 20131127 0257 Safety Report PHHO2012JP017( | PHHO2012JP017066 (eCTD-seq0257) | Safety Report | 0257 |
| IND 109272 | LDK378 | 11/27/2013 | 20131127 0259 Safety Report PHHO2013FR014( | PHHO2013FR014990; (eCTD-seq0259) | Safety Report | 0259 |
| IND 109272 | LDK378 | 11/27/2013 | 20131127 0261 Safety Report PHHO2013JP014: follow-up | PHHO2013JP014373; follow-up (eCTD-seq0261) | Safety Report | 0261 |
| IND 109272 | LDK378 | 11/27/2013 | 20131127 0260 Safety Report PHHO2013FR014( follow-up | PHHO2013FR014506; follow-up (eCTD-seq0260) | Safety Report | 0260 |
| IND 109272 | LDK378 | 11/27/2013 | 20131127 0258 Safety Report PHHO2013US012! Follow-up | PHHO2013US012550; follow-up (eCTD-seq0258) | Safety Report | 0258 |
| IND 109272 | LDK378 | 11/22/2013 | 20131122 0255 Safety Report PHHO2013JP014( | PHHO2013JP014592 (eCTD-seq0255) | Safety Report | 0255 |
| IND 109272 | LDK378 | 11/22/2013 | 20131122 0256 Safety Report PHHO2013DE013: | PHHO2013DE013754 (eCTD-seq0256) | Safety Report | 0256 |
| IND 109272 | LDK378 | 11/19/2013 | 20131119 0253 Safety Report PHHO2013FR014( | PHHO2013FR014506 (eCTD-Seq0253) | Safety Report | 0253 |
| IND 109272 | LDK378 | 11/18/2013 | 20131118 0251 Letter of Authorization | Novartis authorizes the FDA to cross-reference IND 109,272 for LDK378 in support of a compassionate use study to be filed by David Agus, MD. (eCTD-seq0251) | Letter of Authorization | 0251 |
| IND 109272 | LDK378 | 11/15/2013 | 20131115 0252 Safety Report PHHO2013JP014: | PHHO2013JP014373 (eCTD-seq0252) | Safety Report | 0252 |
| IND 109272 | LDK378 | 11/12/2013 | 20131112 0249 Safety Report PHHO2013ES013( Follow-up | PHHO2013ES013524 Follow-up (eCTD-seq0249) | Safety Report | 0249 |
| IND 109272 | LDK378 | 11/12/2013 | 20131112 0250 Safety Report PHHO2013GB009 Follow-up | PHHO2013GB009198 Follow-up (eCTD-seq0250) | Safety Report | 0250 |
| IND 109272 | LDK378 | 11/12/2013 | 20131112 Advice-Information Request iPSP | FDA advice information request regarding meeting on iPSP. | Advice-Information Request | |
| IND 109272 | LDK378 | 11/7/2013 | 20131107 0247 Safety Report PHHY2013NL111( | PHHY2013NL111601; Follow-up (eCTD-seq0247) | Safety Report | 0247 |
| IND 109272 | LDK378 | 11/5/2013 | 20131105 0236 New Investigator CLDK378A2402,C TOO | New Investigators forprotocols CLDK378A2402 and CLDK378A2303. A Transfer of Obligations for Study CLKD378A2303 is also included in this submission. (eCTD-seq0236) | New Investigator | 0236 |
| IND 109272 | LDK378 | 11/5/2013 | 20131105 0246 Safety Report PHHO2013FR014( | PHHO2013FR014035 (eCTD-seq0246) | Safety Report | 0246 |
| | | | | Email from FDA requesting a telecon to discuss possible Novartis involvement in an | | |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 11/4/2013 | 20131104 Email FDA TC Request | ALK master protocol that will test unapproved ALK inhibitors against crizotinib in potential confirmatory studies. | Email | |
| IND 109272 | LDK378 | 11/4/2013 | 20131104 0239 New Protocol CLDK378A2108, TOO | Submission provides new protocol CLDK378A2108. A Transfer of Obligations for Study CLDK378A2108 is also included as part of this submission. (eCTD-seq0239) | New Protocol | 0239 |
| IND 109272 | LDK378 | 11/1/2013 | 20131101 0244 Safety Report PHHO2013TW013 | PHHO2013TW013119; follow-up (eCTD-seq0244) | Safety Report | 0244 |
| IND 109272 | LDK378 | 11/1/2013 | 20131101 0245 Safety Report PHHO2013GB009 | PHHO2013GB009198, followup (eCTD-seq0245) | Safety Report | 0245 |
| IND 109272 | LDK378 | 10/31/2013 | 20131031 0242 Request for Proprietary Name Review Ceralk | Novartis is submitting a "Request for Proprietary Name Review" for Ceralk. (eCTD-seq0242) | General Correspondence | 0242 |
| IND 109272 | LDK378 | 10/31/2013 | 20131031 0243 Safety Report PHHO2013ES013 | PHHO2013ES013524 follwup (eCTD-seq0243) | Safety Report | 0243 |
| IND 109272 | LDK378 | 10/30/2013 | 20131030 Email Studies A2201,A2203 | Email correspondence with FDA in regards to adding information for studies A2201 and A2203 to the NDA. | Email | |
| IND 109272 | LDK378 | 10/30/2013 | 20131030 0241 Safety Report PHHO2013IT0114 Follow-up | PHHO2013IT011464 Follow-up (eCTD-seq0241) | Safety Report | 0241 |
| IND 109272 | LDK378 | 10/30/2013 | 20131030 0240 Safety Report PHHY2013NL111 Follow-up | PHHY2013NL111601 Follow-up (eCTD-seq0240) | Safety Report | 0240 |
| IND 109272 | LDK378 | 10/30/2013 | 20131030 0209 Safety Report PHHO2013US012( | PHHO2013US012052, (eCTD-seq0209) | Safety Report | 0209 |
| IND 109272 | LDK378 | 10/28/2013 | 20131028 0238 Clinical Information Amendment IB Edition 5 | Submission provides IB Edition 5. (eCTD-seq0238) | Clinical Information Amendment | 0238 |
| IND 109272 | LDK378 | 10/27/2013 | 20130927 0207 Safety Report PHHO2013KR008 Follow-up | PHHO2013KR008191 follow-up (eCTD-seq0207) | Safety Report | 0207 |
| IND 109272 | LDK378 | 10/25/2013 | 20131025 Email Follow-up on FDA TC | Email from FDA regarding data from ongoing studies. | Email | |
| IND 109272 | LDK378 | 10/25/2013 | 20131025 0232 Briefing Book Type B | Novartis is submitting the briefing book for the Type B pre-NDA meeting. (eCTD-seq0232) | Briefing Book | 0232 |
| IND 109272 | LDK378 | 10/23/2013 | 20131023 0237 Safety Report PHHO2013TW013 | PHHO2013TW013119; (eCTD-seq0237) | Safety Report | 0237 |
| IND 109272 | LDK378 | 10/21/2013 | 20131021 0230 Change in Protocol CLDK378A2402 Amendment 1 | Amendment 1 to Protocol CLDK378A2402. (eCTD-seq0230) | Change in Protocol | 0230 |
| IND 109272 | LDK378 | 10/21/2013 | 20131021 0224 New Investigator CLDK378X2103,C | New Investigators for protocols CLDK378X2103 and CLDK378A2303. (eCTD-seq0224) | New Investigator | 0224 |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 10/21/2013 | 20131021 0233 Letter of Authorization | Novartis authorizes the FDA to cross-reference to IND 109,272 for LDK378 in support of a compassionate use study to be filed by Derrick Nguyen, MD. (eCTD-seq0233) | Letter of Authorization | 0233 |
| IND 109272 | LDK378 | 10/21/2013 | 20131021 0235 Safety Report PHHO2013KR000 Follow-up | PHHO2013KR000927; follow-up (eCTD-seq0235) | Safety Report | 0235 |
| IND 109272 | LDK378 | 10/18/2013 | 20131018 0234 Safety Report PHHO2013US012( | PHHO2013US012052 (eCTD-seq0234) | Safety Report | 0234 |
| IND 109272 | LDK378 | 10/18/2013 | 20131018 Safety Report PHHY2013NL111( 7-Day | PHHY2013NL111601 7-Day safety report (PS) | Safety Report | |
| IND 109272 | LDK378 | 10/17/2013 | 20131017 0231 Safety Report PHHY2013NL111( | PHHY2013NL111601 (eCTD-seq0231) | Safety Report | 0231 |
| IND 109272 | LDK378 | 10/16/2013 | 20131016 0226 Safety Report PHHO2013US006 | PHHO2013US006144; follow-up (eCTD-seq0226) | Safety Report | 0226 |
| IND 109272 | LDK378 | 10/16/2013 | 20131016 0228 Safety Report PHHO2013US009 | PHHO2013US009217; follow-up9eCTD-seq0228) | Safety Report | 0228 |
| IND 109272 | LDK378 | 10/16/2013 | 20131016 0225 Safety Report PHHO2013US005 | PHHO2013US005829; follow-up (eCTD-seq0225) | Safety Report | 0225 |
| IND 109272 | LDK378 | 10/16/2013 | 20131016 0227 Safety Report PHHO2013US006 Follow-up | PHHO2013US006442 follow-up (eCTD-seq0227) | Safety Report | 0227 |
| IND 109272 | LDK378 | 10/15/2013 | 20131015 0229 Safety Report PHHO2013US009 | PHHO2013US009607; follow-up (eCTD-seq0229) | Safety Report | 0229 |
| IND 109272 | LDK378 | 10/14/2013 | 20131014 0223 Safety Report PHHO2013IT0114 | PHHO2013IT011464 (eCTD-seq0223). | Safety Report | 0223 |
| IND 109272 | LDK378 | 10/14/2013 | 20131014 0218 Safety Report PHHO2013FR012 | PHHO2013FR012599; (eCTD-seq0218) | Safety Report | 0218 |
| IND 109272 | LDK378 | 10/14/2013 | 20131014 0222 Safety Report PHHO2013ES002 | PHHO2013ES002429; follow-up (eCTD-seq0222) | Safety Report | 0222 |
| IND 109272 | LDK378 | 10/11/2013 | 20131011 0221 Safety Report PHHO2013US008 Follow-up | PHHO2013US008426; follow-up (eCTD-seq0221). | Safety Report | 0221 |
| IND 109272 | LDK378 | 10/11/2013 | 20131011 0220 Safety Report PHHO2013US003 | PHHO2013US003591; follow-up (eCTD-seq0220) | Safety Report | 0220 |
| IND 109272 | LDK378 | 10/11/2013 | 20131011 0219 Safety Report PHHO2013IT0095 Follow-up | PHHO2013IT009526; follow-up (eCTD-seq0219) | Safety Report | 0219 |
| IND 109272 | LDK378 | 10/9/2013 | 20131009 0216 Change in Protocol CLDK378X2103 Amendment 2 | Amendment 2 to Protocol CLDK378X2103. (eCTD-seq0216) | Change in Protocol | 0216 |
| IND 109272 | LDK378 | 10/9/2013 | 20131009 OSI Requirements | OSI requests/requirements for NDA/BLA submission. | Other | |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 10/8/2013 | 20131008 0211 Change in Protocol CLDK378X2101 Amendment 6 | Change in protocol for study LDK378X2101 (eCTD-seq0211) | Change in Protocol | 0211 |
| IND 109272 | LDK378 | 10/8/2013 | 20131008 0212 General Correspondence SAP CLDK378X2101 | Novartis is providing the statistical analysis plan for Study CLDK378X2101. (eCTD-seq0212) | General Correspondence | 0212 |
| IND 109272 | LDK378 | 10/8/2013 | 20131008 0217 Safety Report PHHO2013US009( Follow-up | PHHO2013US009607 follow-up (eCTD-seq0217) | Safety Report | 0217 |
| IND 109272 | LDK378 | 10/4/2013 | 20131004 0213 Safety Report PHHO2013US006- Follow-up | PHHO2013US006442; follow-up (eCTD-seq0213) | Safety Report | 0213 |
| IND 109272 | LDK378 | 10/4/2013 | 20131004 0215 Safety Report PHHO2013ES002- Follow-up | PHHO2013ES002429; follow-up (eCTD-seq0215) | Safety Report | 0215 |
| IND 109272 | LDK378 | 10/4/2013 | 20131004 0214 Safety Report PHHO2013US012! | PHHO2013US012550; (eCTD-seq0214) | Safety Report | 0214 |
| IND 109272 | LDK378 | 10/3/2013 | 20131003 Safety Report PHHO2013IT0114 7-Day | PHHO2013IT011464 7-Day safety report (PS) | Safety Report | |
| IND 109272 | LDK378 | 10/2/2013 | 20131002 0210 Safety Report PHHO2013US005! Follow-up | PHHO2013US005829 follow-up (eCTD-seq0210) | Safety Report | 0210 |
| IND 109272 | LDK378 | 9/30/2013 | 20130930 Harmonized DSUR Granted | FDA granted modified reporting period to harmonize DSUR reports for IND 109272 and IND 116381. | Other | |
| IND 109272 | LDK378 | 9/27/2013 | 20130927 0202 New Investigator CLDK378X2103,C | New Investigators for clinical study protocols CLDK378X2103 and CLDK378A2303. (eCTD-seq0202) | New Investigator | 0202 |
| IND 109272 | LDK378 | 9/27/2013 | 20130927 0206 Letter of Authorization | Novartis authorizes the FDA to cross-reference IND 109,272 for LDK378 in support of a compassionate use study to be filed by Kimberly Schlesinger, MD. (eCTD-seq0206) | Letter of Authorization | 0206 |
| IND 109272 | LDK378 | 9/27/2013 | 20130927 0208 Safety Report PHHO2013US008- Follow-up | PHHO2013US008426; follow-up (eCTD-Seq0208) | Safety Report | 0208 |
| IND 109272 | LDK378 | 9/24/2013 | 20130924 0199 Change in Protocol A2301,A2303 Amendment 1 | Protocol amendment - Change in protocol for study CLDK378A2301 & CLDK378A2303 (eCTD-seq0199) | Change in Protocol | 0199 |
| IND 109272 | LDK378 | 9/24/2013 | 20130924 0203 Safety Report PHHO2013US006- Follow-Up | PHHO2013US006452 follow-up (eCTD-0203) | Safety Report | 0203 |
| IND 109272 | LDK378 | 9/24/2013 | 20130924 0205 Safety Report PHHO2013IT0084 | PHHO2013IT008415; follow-up (eCTD-seq0205) | Safety Report | 0205 |
| | | | 20130924 0204 | | | |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 9/24/2013 | Safety Report PHHO2013US012( | PHHO2013US012052; (eCTD-seq0204) | Safety Report | 0204 |
| IND 109272 | LDK378 | 9/19/2013 | 20130919 0201 Safety Report PHHO2013IT0095 | PHHO2013IT009526; follow-up (eCTD-seq0201) | Safety Report | 0201 |
| IND 109272 | LDK378 | 9/17/2013 | 20130917 Meeting Request Granted Type B 20131122 | FDA granting request for a Tpye B meeting scheduled for November 22, 2013 to discuss the content of the NDA and content and format of the Safety and Efficacy Update. | Other | |
| IND 109272 | LDK378 | 9/17/2013 | 20130917 0200 Safety Report PHHO2013ES002- Follow-Up | | Safety Report | 0200 |
| IND 109272 | LDK378 | 9/16/2013 | 20130916 0197 Change in Protocol A2201,A2203 Amendment 2 | Amendment 2 to Protocols CLDK378A2201 & CLDK378A2203. (eCTD-seq0197) | Change in Protocol | 0197 |
| IND 109272 | LDK378 | 9/16/2013 | 20130916 0198 Safety Report PHHO2013JP0107 Follow-up | PHHO2013JP010761 follow-up (eCTD-seq0198) | Safety Report | 0198 |
| IND 109272 | LDK378 | 9/11/2013 | 20130911 0195 General Correspondence Table of Contents | Novartis is requesting input on the TOC, as opposed to the pre-NDA meeting, to help facilitate the submission process which will begin prior to the pre-NDA meeting. (eCTD-seq0195) | General Correspondence | 0195 |
| IND 109272 | LDK378 | 9/10/2013 | 20130910 0193 New Investigator CLDK378A2402,C | | New Investigator | 0193 |
| IND 109272 | LDK378 | 9/10/2013 | 20130910 0188 New Protocol CLDK378A2110 TOO | Submission provides New Protocol CLDK378A2110 and TOO. (eCTD-seq0188) | New Protocol | 0188 |
| IND 109272 | LDK378 | 9/10/2013 | 20130910 0196 Safety Report PHHO2013IT0095 | PHHO2013IT009526; follow-up (eCTD-seq0196) | Safety Report | 0196 |
| IND 109272 | LDK378 | 9/6/2013 | 20130906 Safety Report PHHO2013US009( 7-Day | PHHO2013US009607 7-Day safety report (PS) | Safety Report | |
| IND 109272 | LDK378 | 9/5/2013 | 20130905 0194 Waiver Request Pediatric Studies | Waiver request for pediatric studies. (eCTD-seq0194) | Other | 0194 |
| IND 109272 | LDK378 | 9/5/2013 | 20130905 Advice-Information Request Portions | FDA agreeing with Novartis' plan for submision of portions for review of their planned NDA for LDK378. | Advice-Information Request | |
| IND 109272 | LDK378 | 9/3/2013 | 20130903 0190 Safety Report PHHO2013ES007- | PHHO2013ES007451; follow-up (eCTD-seq0190) | Safety Report | 0190 |
| IND 109272 | LDK378 | 9/3/2013 | 20130903 0192 Safety Report PHHO2013KR010; Follow up | PHHO2013KR010255 follow uip (eCTD-seq0192) | Safety Report | 0192 |
| IND 109272 | LDK378 | 9/3/2013 | 20130903 0191 Safety Report PHHO2013JP0107 Follow up | PHHO2013JP010761 follow up (eCTD-seq0191) | Safety Report | 0191 |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 8/30/2013 | 20130830 0186 Safety Report PHHO2013JP009( Follow up | PHHO2013JP009095 follow up (eCTD-seq0186) | Safety Report | 0186 |
| IND 109272 | LDK378 | 8/29/2013 | 20130829 0189 Safety Report PHHO2013U2005 | PHHO2013U2005829; follow-up (eCTD-seq0189) | Safety Report | 0189 |
| IND 109272 | LDK378 | 8/28/2013 | 20130828 0183 Additional Authorized Contact | Submission is to inform FDA that effective immediately Denisa Weinstein will be an additional authorized contact for IND 109,272 Study CLDK378X2103. (eCTD-seq0183) | General Correspondence | 0183 |
| IND 109272 | LDK378 | 8/28/2013 | 20130828 0187 Safety Report PHHO2013ES002 | PHHO2013ES002429; follow-up (eCTD-seq0187) | Safety Report | 0187 |
| IND 109272 | LDK378 | 8/27/2013 | 20130827 0184 Request for FDA Mtg Type B | Request for a Type B meeting with FDA to further discuss the NDA submission for LDK378. (eCTD-seq0184) | Request for FDA Mtg | 0184 |
| IND 109272 | LDK378 | 8/26/2013 | 20130826 0181 New Investigator A2203,A2303,X21 | New Investigators for clinical study protocols CLDK378A2203, CLDK378A2303 and CLDK378X2103. (eCTD-seq0181) | New Investigator | 0181 |
| IND 109272 | LDK378 | 8/24/2013 | 20130824 0185 Safety Report PHHO2013JP0107 | PHHO2013JP010761 (eCTD Seq 0185) | Safety Report | 0185 |
| IND 109272 | LDK378 | 8/20/2013 | 20130409 0099 Safety Report PHH02013NL004 | PHH02013NL004408 (eCTD-seq0099) | Safety Report | 0099 |
| IND 109272 | LDK378 | 8/20/2013 | 20130820 0182 Safety Report PHHO2013US009( Follow-up | PHHO2013US009607 Follow-Up (eCTD-seq0182) | Safety Report | 0182 |
| IND 109272 | LDK378 | 8/16/2013 | 20130816 0178 Safety Report PHHO2013KR010 | PHHO2013KR010255 (eCTD-Seq0178) | Safety Report | 0178 |
| IND 109272 | LDK378 | 8/16/2013 | 20130816 0179 Safety Report PHHO2013IT0095 Follow-Up | PHHO2013IT009526; follow-up (eCTD-Seq0179) | Safety Report | 0179 |
| IND 109272 | LDK378 | 8/16/2013 | 20130816 0180 Safety Report PHHO2013NL004 Follow-Up | PHHO2013NL004408; follow-up (eCTD-Seq0180) | Safety Report | 0180 |
| IND 109272 | LDK378 | 8/15/2013 | 20130815 0177 Safety Report PHHO2013US006 Follow-Up | PHHO2013US006204; follow-up (eCTD-Seq0177) | Safety Report | 0177 |
| IND 109272 | LDK378 | 8/14/2013 | 20130814 Meeting Request Written Responses | FDA written responses to questions for the Type C meeting discuss the content and format of the NDA submission for LDK378 in the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received prior treatment with crizotinib. | Meeting Request Written Responses | |
| IND 109272 | LDK378 | 8/12/2013 | 20130812 0176 General Correspondence Request for Waiver of PSR | Novartis is re-submitting a request for a disease-specific waiver from conducting trials with LDK378 in pediatric patients with ALK-positive NSCLC using FDA's new template. (eCTD-seq0176) | General Correspondence | 0176 |
| IND 109272 | LDK378 | 8/9/2013 | 20130809 0175 Safety Report PHHO2013JP009( | PHHO2013JP009095; follow-up (eCTD-seq0175) | Safety Report | 0175 |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 8/9/2013 | 20130809 0172 Safety Report PHHO2013US008 | PHHO2013US008426; follow-up (eCTD-seq0172) | Safety Report | 0172 |
| IND 109272 | LDK378 | 8/8/2013 | 20130808 0174 Safety Report PHHO2013US009 | PHHO2013US009217; follow-up (eCTD-seq0174) | Safety Report | 0174 |
| IND 109272 | LDK378 | 8/8/2013 | 20130808 0170 Safety Report PHHO2013IT0095 | PHHO2013IT009526; follow-up (eCTD-seq0170) | Safety Report | 0170 |
| IND 109272 | LDK378 | 8/8/2013 | 20130808 0171 Safety Report PHHO2013ES007 | PHHO2013ES007451; follow-up (eCTD-seq0171) | Safety Report | 0171 |
| IND 109272 | LDK378 | 8/7/2013 | 20130807 0173 Safety Report PHHO2013US006 Follow-up | PHHO2013US006142 Follow-up (eCTD-seq0173) | Safety Report | 0173 |
| IND 109272 | LDK378 | 8/5/2013 | 20130805 0167 New Investigator CLDK378A2201,C | New Investigators for Protocols CLDK378A2201 and CLDK378A2303. (eCTD-seq0167) | New Investigator | 0167 |
| IND 109272 | LDK378 | 8/5/2013 | 20130805 0169 Safety Report PHHO2013JP009( | PHHO2013JP009095 (eCTD-seq0169) | Safety Report | 0169 |
| IND 109272 | LDK378 | 8/2/2013 | 20130802 Advice-Information Request Safety | FDA is requesting that Novartis make modifications to their ongoing and planned clinical trials as well as the IB. | Advice-Information Request | |
| IND 109272 | LDK378 | 8/1/2013 | 20130801 0163 General Correspondence Update Phase III Trials A2301,A2304 | Novartis is providing an update on two phase III trials (A2301) and (A2304) in previously untreated patients with ALK-positive NSCLC. (eCTD-seq0163) | General Correspondence | 0163 |
| IND 109272 | LDK378 | 8/1/2013 | 20130801 0168 Safety Report PHHO2013GB009 | PHHO2013GB009198; follow-up (eCTD-seq0168) | Safety Report | 0168 |
| IND 109272 | LDK378 | 7/31/2013 | 20130731 0162 General Correspondence Notification of SUSARs | Novartis is informing the Agency of four select suspected, unexpected serious adverse reactions (SUSARs), which have been recently reported in the LDK378 clinical program after preparation of the current Investigator's Brochure (which provides data up to 29-Apr-2013). (eCTD-seq0162) | General Correspondence | 0162 |
| IND 109272 | LDK378 | 7/31/2013 | 20130731 0165 Safety Report PHHO2013NL004 Follow-up | PHHO2013NL004408 Follow-Up (eCTD-seq0165) | Safety Report | 0165 |
| IND 109272 | LDK378 | 7/29/2013 | 20130729 0161 Response to FDA Request 20130718 Written Responses | Novartis is providing a response to FDA's feedback that was provided in the written responses dated July 18, 2013. Novartis believes that FDA's response to Question 4 requires further clarification. (eCTD-seq0161) | Response to FDA Request | 0161 |
| IND 109272 | LDK378 | 7/29/2013 | 20130730 0166 Safety Report PHHO2013KR008 | PHHO2013KR008644; follow-up (eCTD-seq0166) | Safety Report | 0166 |
| IND 109272 | LDK378 | 7/29/2013 | 20130729 0156 Safety Report PHHO2013GB009 | PHHO2013GB009198 (eCTD-seq0156) | Safety Report | 0156 |
| IND 109272 | LDK378 | 7/26/2013 | 20130726 0164 Safety Report | PHHO2013IT009526 (eCTD-seq0164) | Safety Report | 0164 |

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|---|---|---|---|---|---|---|
| | | | PHHO2013IT0095 | | | |
| IND 109272 | LDK378 | 7/26/2013 | 20130726 0160 Safety Report PHHO2013IT0084 | PHHO2013IT008415 (eCTD-seq0160) | Safety Report | 0160 |
| IND 109272 | LDK378 | 7/25/2013 | 20130725 0155 CMC Information Amendment | Novartis is submitting an Information Amendment to provide for specific updates to drug substance and drug product sections to support the current clinical trials in phase I, II and III. (eCTD-seq0155) | CMC Information Amendment | 0155 |
| IND 109272 | LDK378 | 7/24/2013 | 20130724 0157 Safety Report PHHO2013US009217 | PHHO2013US009217 (eCTD-seq0157) | Safety Report | 0157 |
| IND 109272 | LDK378 | 7/24/2013 | 20130724 0158 Safety Report PHHO2013US008426 Follow-up | PHHO2013US008426 Follow-Up (eCTD-seq0158) | Safety Report | 0158 |
| IND 109272 | LDK378 | 7/19/2013 | 20130719 0154 General Correspondence Rolling Review Request | Novartis is requesting that FDA consider a rolling submission for LDK378. (eCTD-seq0154) | General Correspondence | 0154 |
| IND 109272 | LDK378 | 7/18/2013 | 20130718 0148 New Investigator CLDK378A2201 CLDK378A2303 | New Investigators for Protocols CLDK378A2201 and CLDK378A2303. (eCTD-seq0148) | New Investigator | 0148 |
| IND 109272 | LDK378 | 7/18/2013 | 20130718 Meeting Request Written Responses | FDA written responses to questions contained in the March 21, 2013 background package. | Meeting Request Written Responses | |
| IND 109272 | LDK378 | 7/18/2013 | 20130718 Safety Report PHHO2013IT0084 7-day | PHHO2013IT008415 7-day safety report. (PS) | Safety Report | |
| IND 109272 | LDK378 | 7/17/2013 | 20130717 0152 Safety Report PHHO2013JP008( Follow-up | PHHO2013JP008089 Follow-Up (eCTD-seq0152) | Safety Report | 0152 |
| IND 109272 | LDK378 | 7/17/2013 | 20130717 0153 Safety Report PHHO2013KR008( Follow-up | PHHO2013KR008644 Follow-Up (eCTD-seq0153) | Safety Report | 0153 |
| IND 109272 | LDK378 | 7/12/2013 | 20130712 0150 Statistical Analysis Plan CLDK378X2101 | Submission provides the statistical analysis plan for Study CLDK378X2101. (eCTD-seq0150) | General Correspondence | 0150 |
| IND 109272 | LDK378 | 7/12/2013 | 20130712 0151 Safety Report PHHO2013KR008 | PHHO2013KR008191; follow-up (eCTD-seq0151) | Safety Report | 0151 |
| IND 109272 | LDK378 | 7/10/2013 | 20130710 Meeting Request Cancellation and Preliminary Comments | FDA letters regarding the cancellation of the Type B meeting scheduled for May 14, 2013 along with Preliminary responses to Novartis meeting questions. | Other | |
| IND 109272 | LDK378 | 7/10/2013 | 20130710 0149 Safety Report PHHO2013JP008( | PHHO2013JP008089; follow-up (eCTD-seq0149) | Safety Report | 0149 |
| IND 109272 | LDK378 | 7/10/2013 | 20130710 0159 Safety Report PHHO2013KR008 Follow-up | PHHO2013KR008191 Follow-Up (eCTD-seq0159) | Safety Report | 0159 |
| | | | 20130709 0145 | | | |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 7/9/2013 | Safety Report PHHO2013NL006 Follow-up | PHHO2013NL006726 Follow-Up (eCTD-seq0145) | Safety Report | 0145 |
| IND 109272 | LDK378 | 7/9/2013 | 20130709 0146 Safety Report PHHO2013KR008 | PHHO2013KR008644 (eCTD-Seq0146) | Safety Report | 0146 |
| IND 109272 | LDK378 | 7/9/2013 | 20130709 0147 Safety Report PHHO2013US006 Follow-up | PHHO2013US006144 Follow-Up (eCTD-seq0147) | Safety Report | 0147 |
| IND 109272 | LDK378 | 7/8/2013 | 20130708 Email FDA Comments on ETP Protocol | Email from FDA with comments on ETP protocol. | Email | |
| IND 109272 | LDK378 | 7/8/2013 | 20130708 Acknowledge Treatment Protocol | FDA acknowledgement of treatment protocol CLDK378A2402. | Other | |
| IND 109272 | LDK378 | 7/5/2013 | 20130705 0144 Safety Report PHHO2013KR008 | PHHO2013KR008191 (eCTD-seq0144) | Safety Report | 0144 |
| IND 109272 | LDK378 | 7/5/2013 | 20130705 0143 Safety Report PHHO2013US008 | PHHO2013US008426 (eCTD-seq0053) | Safety Report | 0143 |
| IND 109272 | LDK378 | 7/3/2013 | 20130703 0142 Safety Report PHHO2013JP007 Follow-Up | PHHO2013JP007602 (eCTD-seq0142). | Safety Report | 0142 |
| IND 109272 | LDK378 | 7/2/2013 | 20130702 0139 Safety Report PHHO2013US001 Follow-up | PHHO2013US001989 Follow-Up (eCTD-seq0139) | Safety Report | 00139 |
| IND 109272 | LDK378 | 7/2/2013 | 20130702 0141 Safety Report PHHO2013ES007 | PHHO2013ES007451 (eCTD-seq0141) | Safety Report | 0141 |
| IND 109272 | LDK378 | 7/1/2013 | 20130701 0135 Clinical Information Amendment | Clinical Information Amendment 'Novartis is submiting Edition 4 of the LDK378 Investigator's Brochure dated 28-Jun-2013' (eCTD-seq0135) | Clinical Information Amendment | 0135 |
| IND 109272 | LDK378 | 6/28/2013 | 20130628 0137 Response to FDA Request 20130627 Email | Response to FDA email request dated June 27, 2013 requesting that Novartis submit the informed consent document for Study CLDK378A2402. (eCTD-seq0137) | Response to FDA Request | 0137 |
| IND 109272 | LDK378 | 6/28/2013 | 20130628 0138 Safety Report PHHO2013JP008 | PHHO2013JP008089 (eCTD-seq0138) | Safety Report | 0138 |
| IND 109272 | LDK378 | 6/27/2013 | 20130627 0132 New Investigator CLDK378A2201 CLDK378A2203 | New Investigators for Protocol CLDK378A2201 and CLDK378A2203. (eCTD-seq0132) | New Investigator | 0132 |
| IND 109272 | LDK378 | 6/27/2013 | 20130627 0136 Safety Report PHHO2013JP007 Follow-up | PHHO2013JP007602 Follow-Up (eCTD-seq0136) | Safety Report | 0136 |
| IND 109272 | LDK378 | 6/25/2013 | 20130625 0124 Safety Report PHHO2013ES002 Follow-up | PHHO2013ES002429 Follow-Up (eCTD-seq0124) The receipts are not available for this submission. | Safety Report | 0124 |
| IND 109272 | LDK378 | 6/25/2013 | 20130625 0134 Safety Report PHHO2013US006 Follow-up | PHHO2013US006144 Follow-Up (eCTD-seq0134) | Safety Report | 0134 |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 6/24/2013 | 20130624 0130 Letter of Authorization | Novartis authorizes the FDA to cross-reference to IND 109,272 for LDK378 in support of a study to be filed by sponsor Howard (Jack)West, MD Medical Oncologist Swedish Cancer Institute 1221 Madison St., Suite 200 Seattle, WA 98104. (eCTD-seq0130) | Letter of Authorization | 0130 |
| IND 109272 | LDK378 | 6/24/2013 | 20130624 0131 Response to FDA Request 20130620 Email | Response to FDA email request dated June 20, 2013 regarding expanded treatment Protocol CLDK378A2402. (eCTD-seq0131) | Response to FDA Request | 0131 |
| IND 109272 | LDK378 | 6/24/2013 | 20130624 0133 Safety Report PHHO2013US006 | PHHO2013US006442 (eCTD-seq0133) | Safety Report | 0133 |
| IND 109272 | LDK378 | 6/21/2013 | 20130621 0126 Additional Authorized Contact | Submission is to inform FDA that effective immediately Yanina (Nina) Gutman will be an additional authorized contact for IND 109,272 (LDK378). (eCTD-seq0126) | General Correspondence | 0126 |
| IND 109272 | LDK378 | 6/20/2013 | 20130620 Email FDA Request Treatment Protocol | Email request from FDA asking Novartis to provide an updated list of all proposed manufacturing, labeling, testing and packaging sites to be used for clinical supplies of the investigational drug substance and drug product. | Email | |
| IND 109272 | LDK378 | 6/19/2013 | 20130619 0128 Safety Report PHHO2013NL006 Follow-up | PHHO2013NL006726 Follow-Up (eCTD-seq0128) | Safety Report | 0128 |
| IND 109272 | LDK378 | 6/19/2013 | 20130619 0129 Safety Report PHHO2013JP007 | PHHO2013JP007602 Follow-Up (eCTD-seq0129) | Safety Report | 0129 |
| IND 109272 | LDK378 | 6/18/2013 | 20130618 0127 Safety Report PHHO2013JP007 Follow-up | PHHO2013JP007313 Follow-Up (eCTD-seq0127) | Safety Report | 0127 |
| IND 109272 | LDK378 | 6/13/2013 | 20130613 Email Proprietary Name Submission | Email question from FDA asking when Novartis will submit a Request for Proprietary Name Review. | Email | |
| IND 109272 | LDK378 | 6/13/2013 | 20130613 0125 Safety Report PHHO2013JP007 | PHHO2013JP007313 (eCTD-seq0125) | Safety Report | 0125 |
| IND 109272 | LDK378 | 6/12/2013 | 20130612 0121 New Protocol CLDK378A2402 | New Protocol CLDK378A2402, entitled "An open-label, multi-center, Expanded Treatment Protocol (ETP) of oral LDK378 in adult patients with non-small cell lung cancer (NSCLC) characterized by ALK(+) rearrangements in patients previously treated with an ALK inhibitor.." (eCTD-seq0121). | New Protocol | 0121 |
| IND 109272 | LDK378 | 6/12/2013 | 20130612 0123 Safety Report PHHO2013FR054 | PHHO2013FR054848 (eCTD-seq0123) | Safety Report | 0123 |
| IND 109272 | LDK378 | 6/11/2013 | 20130611 0122 General Correspondence Request for Waiver of PSR | Novartis is requesting a full waiver from conducting pediatric studies as the pathophysiology of ALK-positive NSCLC limits the disease to the adult population, and therefore, LDK378 qualifies for a disease-specific waiver. (eCTD-seq0122) | General Correspondence | 0122 |
| IND 109272 | LDK378 | 6/10/2013 | 20130610 0119 NVS Responses to FDA Comments | Novartis responses to FDA comments received on May 20, 2013. (eCTD-seq0119) | General Correspondence | 0119 |

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|---|---|---|---|---|---|---|
| | | | 20130520 | | | |
| IND 109272 | LDK378 | 6/7/2013 | 20130607 0120 Safety Report PHHO2013NL004 | PHHO2013NL004408; follow-up (eCTD-seq0120) | Safety Report | 0120 |
| IND 109272 | LDK378 | 6/6/2013 | 20130606 HA Mtg Minutes Type B 20130515 | FDA minutes from the Type B meeting held on May 15, 2013 to discuss the clinical development program of LDK378 in previously untreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. | HA Mtg Minutes | |
| IND 109272 | LDK378 | 6/5/2013 | 20130605 0117 New Investigator A2201 A2303 X2103 | New Investigator(s) for Protocol CLDK378A2201, CLDK378A2303 and CLDK378X2103 (eCTD-seq0117) | New Investigator | 0117 |
| IND 109272 | LDK378 | 5/31/2013 | 20130531 0118 Safety Report PHHO2013NL006 | PHHO2013NL006726 (eCTD-seq0118) | Safety Report | 0118 |
| IND 109272 | LDK378 | 5/22/2013 | 20130522 0116 Safety Report PHHO2013US006 | PHHO2013US006452 (eCTD-seq0116) | Safety Report | 0116 |
| IND 109272 | LDK378 | 5/21/2013 | 20130521 0114 Safety Report PHHO2013US006 | PHHO2013US006144 (eCTD-seq0114) | Safety Report | 0114 |
| IND 109272 | LDK378 | 5/21/2013 | 20130521 0115 Safety Report PHHO2013US006 | PHHO2013US006142 (eCTD-seq0115) | Safety Report | 0115 |
| IND 109272 | LDK378 | 5/20/2013 | 20130520 0110 New Investigator CLDK378A2201, A2106, A2203 | New INvestigator(s) for Protocol CLDK378A2201, CLDK378A2106 and CLDK378A2203 | New Investigator | 0110 |
| IND 109272 | LDK378 | 5/20/2013 | 20130520 0113 Safety Report PHHO2012NZ006 | PHHO2012NZ006303; follow-up (eCTD-seq0113) | Safety Report | 0113 |
| IND 109272 | LDK378 | 5/16/2013 | 20130516 0111 Safety Report PHHO2013US005 | PHHO2013US005829; follow-up (eCTD-seq0111) | Safety Report | 0111 |
| IND 109272 | LDK378 | 5/16/2013 | 20130516 0112 Safety Report PHHO2013US006 | PHHO2013US006204 (eCTD-seq0112) | Safety Report | 0112 |
| IND 109272 | LDK378 | 5/15/2013 | 20130515 Mtg Minutes EOP2 | Novartis minutes from the EOP2 meeting dated May 15, 2013. | Mtg Minutes | |
| IND 109272 | LDK378 | 5/3/2013 | 20130503 0108 New Investigator CLDK378A2201 & CLDK378A2203 | New Investigator for Protocols CLDK378A2201 and CLDK378A2203 (eCTD-seq0108) | New Investigator | 0108 |
| IND 109272 | LDK378 | 5/2/2013 | 20130502 0107 Change in Protocol CLDK378X2101 Amendment 5 | Amendment 5 to Protocol CLDK378X2101. (eCTD-seq0107) | Change in Protocol | 0107 |
| IND 109272 | LDK378 | 4/25/2013 | 20130425 0105 Response to FDA Request 20130409 | Response to FDA request dated April 9, 2013 regarding two drug-drug interaction studies, Studies CLDK378A2104 and CLDK378A2106. (eCTD-seq0105) | Response to FDA Request | 0105 |
| IND 109272 | LDK378 | 4/22/2013 | 20130422 0096 New Investigator | New Investigators for CLDK378A2201 and | New | 0096 |

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|---|---|---|---|---|---|---|
| | | | CLDK378A2201 CLDK378A2203 | CLDK378A2203. (eCTD-seq0096) | Investigator | |
| IND 109272 | LDK378 | 4/19/2013 | 20130419 0104 Safety Report PHHO2013JP004 | PHHO2013JP004555; follow-up (eCTD-seq0104) | Safety Report | 0104 |
| IND 109272 | LDK378 | 4/19/2013 | 20130419 0106 Safety Report PHHO2013JP004 | PHHO2013JP004554; follow-up (eCTD-seq0106) | Safety Report | 0106 |
| IND 109272 | LDK378 | 4/17/2013 | 20130417 0100 Briefing Book Type C | Novartis is submitting a briefing book for a Type C meeting to gain agreement on the content and format of the proposed NDA with the Agency. (eCTD-seq0100) | Briefing Book | 0100 |
| IND 109272 | LDK378 | 4/15/2013 | 20130415 0109 Safety Report PHHO2013US004 Follow-up | PHHO2013US004353 Follow-Up (eCTD-seq0109) | Safety Report | 0109 |
| IND 109272 | LDK378 | 4/12/2013 | 20130412 0103 Briefing Book Type B CMC 20130514 | Novartis is submitting the CMC briefing book for the Type B meeting scheduled for May 14, 2013. (eCTD-seq0103) | Briefing Book | 0103 |
| IND 109272 | LDK378 | 4/12/2013 | 20130412 0098 Briefing Book Type B EOP2 20130515 | Novartis is submitting the briefing book for the Type B EOP2 meeting scheduled for May 15, 2013 to discuss the clinical development program of LDK378 in previously untreated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. (eCTD-seq0098) | Briefing Book | 0098 |
| IND 109272 | LDK378 | 4/12/2013 | 20130412 0102 Safety Report PHHO2013JP004 | PHHO2013JP004555; follow-up (eCTD-seq0102) | Safety Report | 0102 |
| IND 109272 | LDK378 | 4/11/2013 | 20130411 0093 Change in Protocol CLDK378A2203 Amendment 2 | Amendment 2 to Protocol CLDK378A2203. (eCTD-seq0093) | Change in Protocol | 0093 |
| IND 109272 | LDK378 | 4/11/2013 | 20130411 0101 Safety Report PHH02013JP0045 | PHH02013JP004554 (eCTD-seq0101) | Safety Report | 0101 |
| IND 109272 | LDK378 | 4/9/2013 | 20130409 Meeting Request Grant Written Response Type B 20130515 | FDA granting request for a Type B meeting scheduled for May 15, 2013 to discuss the clinical development program of LDK378 in previously untreated patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. | Meeting Request Grant Written Response | |
| IND 109272 | LDK378 | 4/9/2013 | 20130409 Advice-Information Request | FDA information request regarding two drug-drug interaction study protocols. | Advice-Information Request | |
| IND 109272 | LDK378 | 4/8/2013 | 20130408 0097 Safety Report PHHO2013US004 | PHHO2013US004353 (eCTD-seq0097) | Safety Report | 0097 |
| IND 109272 | LDK378 | 4/5/2013 | 20130405 0092 Change in Protocol CLDK378A2201 Amendment1 | Amendment 1 to Study CLDK378A2201 (eCTD-seq0092) | Change in Protocol | 0092 |
| IND 109272 | LDK378 | 4/5/2013 | 20130405 0094 Safety Report PHHO2013KR004 | PHHO2013KR004341 (eCTD-seq0094) | Safety Report | 0094 |
| | | | 20130404 0091 | New Protocol Study CLDK378A2303. (eCTD- | | |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 4/4/2013 | New Protocol CLDK378A2303 | seq0091) | New Protocol | 0091 |
| IND 109272 | LDK378 | 4/4/2013 | 20130404 0095 Safety Report PHHO2013US003 | PHHO2013US003591 (eCTD-seq0095) | Safety Report | 0095 |
| IND 109272 | LDK378 | 4/1/2013 | 20130401 Safety Report PHHO2013US004 7-day | PHHO2013US004353 7-day safety report. (PS) | Safety Report | |
| IND 109272 | LDK378 | 3/29/2013 | 20130329 0089 Change in Protocol CLDK378X2103 Amendment 1 | Amendment 1 to Study CLDK378X2103. (eCTD-seq0089) | Change in Protocol | 0089 |
| IND 109272 | LDK378 | 3/29/2013 | 20130329 0088 New Protocol CLDK378A2104 CLDK378A2106 | New Protocols CLDK378A2104, CLDK378A2106. (eCTD-seq0088) | New Protocol | 0088 |
| IND 109272 | LDK378 | 3/27/2013 | 20130327 0090 Safety Report PHHO2013US003 | PHHO2013US003591 (eCTD-seq0090) | Safety Report | 0090 |
| IND 109272 | LDK378 | 3/26/2013 | 20130326 0087 New Investigator CLDK378A2201 | New Investigator for Protocol CLDK378A2201. (eCTD-seq0087) | New Investigator | 0087 |
| IND 109272 | LDK378 | 3/22/2013 | 20130322 Meeting Request Grant Written Response Type B | FDA letter granting request for a Type B meeting discuss the clinical development program of LDK378 in previously untreated patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. | Meeting Request Grant Written Response | |
| IND 109272 | LDK378 | 3/18/2013 | 20130318 0086 Request for FDA Mtg Type B CMC Specific | Novartis respectfully requests a Type B, CMC specific, pre-NDA meeting to obtain FDA guidance on the following topics: 1. Agreement on drug substance starting materials in the NDA. 2. Agreement to submit the NDA with 6-9 months stability data for three drug substance batches as part of the registration stability package. 3. Agreement to submit the NDA with 3-6 months stability data for three drug product batches as part of the registration stability package. (eCTD-seq0086) | Request for FDA Mtg | 0086 |
| IND 109272 | LDK378 | 3/15/2013 | 20130315 Meeting Request Grant Written Response Type C | FDA written responses only to meeting request for Type C meeting. | Meeting Request Grant Written Response | |
| IND 109272 | LDK378 | 3/11/2013 | 20130311 0085 Safety Report PHHO2012JP016 | PHHO2012JP016929; follow-up (eCTD-seq0085) | Safety Report | 0085 |
| IND 109272 | LDK378 | 3/6/2013 | 20130306 Grant Breakthrough Therapy Designation | FDA letter granting Breakthrough Therapy designation. | Other | |
| IND 109272 | LDK378 | 3/6/2013 | 20130306 0084 Safety Report PHHO2013ES002 | PHHO2013ES002429; follow-up (eCTD-seq0084) | Safety Report | 0084 |
| IND 109272 | LDK378 | 3/4/2013 | 20130304 0083 CMC Information Amendment | Novartis is submitting an CMC Amendment to provide for the following changes to Module 3 drug substance and drug product sections to support the current clinical | CMC Information Amendment | 0083 |

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|---|---|---|---|---|---|---|
| | | | | trials in phase II and III. (eCTD-seq0083) | | |
| IND 109272 | LDK378 | 3/1/2013 | 20130301 0081 Request for FDA Mtg Type B | Request for a Type B meeting with the Agency to discuss the clinical development program of LDK378 in previously untreated patients with locally advanced or metastatic nonsmall cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive. (eCTD-seq0081) | Request for FDA Mtg | 0081 |
| IND 109272 | LDK378 | 2/27/2013 | 20130227 0080 General Correspondence CDRH Submission | Novartis is providing the information that was submitted to CDRH via email regarding question 5 from the November 20, 2013 CDER/CDRH meeting. (eCTD-seq0080) | General Correspondence | 0080 |
| IND 109272 | LDK378 | 2/26/2013 | 20130226 0076 New Investigator CLDK378X2101 | New investigator for study protocol CLDK378X2101 (eCTD-seq0076) | New Investigator | 0076 |
| IND 109272 | LDK378 | 2/26/2013 | 20130226 0079 Safety Report PHHO2012DE016 | PHHO2012DE016261; follow-up (eCTD-seq0079) | Safety Report | 0079 |
| IND 109272 | LDK378 | 2/22/2013 | 20130222 0077 Request for FDA Mtg Type C | Novartis is requesting a Type C meeting with the Agency to discuss the content and format of the NDA submission for LDK378. (eCTD-seq0077) | Request for FDA Mtg | 0077 |
| IND 109272 | LDK378 | 2/22/2013 | 20130222 0078 Safety Report PHHO2013ES002 | PHHO2013ES002429 (eCTD-seq0078) | Safety Report | 0078 |
| IND 109272 | LDK378 | 2/21/2013 | 20130221 0082 Safety Report PHHO2012JP016 Follow-up | PHHO2012JP016929 Follow-Up (eCTD-seq0082) | Safety Report | 0082 |
| IND 109272 | LDK378 | 2/20/2013 | 20130220 0074 Safety Report PHHO2012JP016 | PHHO2012JP016929; follow-up (eCTD-seq0074) | Safety Report | 0074 |
| IND 109272 | LDK378 | 2/20/2013 | 20130220 0075 Safety Report PHHO2013KR000 | PHHO2013KR000927; follow-up (eCTD-seq0075) | Safety Report | 0075 |
| IND 109272 | LDK378 | 2/15/2013 | 20130215 0072 Response to FDA Request 20130212 Email | Response to FDA email request dated February 12, 2013 regarding the Breakthrough Therapy Designation. (eCTD-seq0072) | Response to FDA Request | 0072 |
| IND 109272 | LDK378 | 2/15/2013 | 20130215 0073 Safety Report PHHO2013US001 | PHHO2013US001989 (eCTD-seq0073) | Safety Report | 0073 |
| IND 109272 | LDK378 | 2/14/2013 | 20130214 0071 New Protocol CLDK378A2104 CLDK378A2106 | New Protocols CLDK378A2104, CLDK378A2106. (eCTD-seq0071) | New Protocol | 0071 |
| IND 109272 | LDK378 | 2/12/2013 | 20130212 Email Breakthrough Therapy | Email request from FDA regarding Breakthrough Therapy. | Email | |
| IND 109272 | LDK378 | 2/6/2013 | 20130206 0070 New Investigator CLDK378A2105 | New Investigator(s) for protocol(s) CLDK378A2105 (eCTD-seq0070) | New Investigator | 0070 |
| IND 109272 | LDK378 | 2/5/2013 | 20130205 0069 Response to FDA Request Email | Response to FDA email request regarding Study CLDK378X2103. (eCTD-seq0069) | Response to FDA Request | 0069 |
| IND 109272 | LDK378 | 2/1/2013 | 20130201 0068 Change in Protocol CLDK378X2101 | Amendment 4 Study CLDK378X2101. Also included is a TOO. (eCTD-seq0068) | Change in Protocol | 0068 |

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|---|---|---|---|---|---|---|
| | | | TOO | | | |
| IND 109272 | LDK378 | 1/31/2013 | 20130131 Email Study May Proceed | Email from FDA notifying Novartis that FDA has completed the review for protocol CLDK378X2103 and determined that you may proceed with your study. | Email | |
| IND 109272 | LDK378 | 1/24/2013 | 20130124 0066 Safety Report PHHO2013KR000 | PHHO2013KR000927 (eCTD-seq0066) | Safety Report | 0066 |
| IND 109272 | LDK378 | 1/24/2013 | 20130124 0067 Safety Report PHHO2012JP016 | PHHO2012JP016929; follow-up (eCTD-seq0067) | Safety Report | 0067 |
| IND 109272 | LDK378 | 1/18/2013 | 20130118 Advice-Information Request Clinical | FDA information request regarding Novartis request for Breakthrough Therapy Designation. | Advice-Information Request | |
| IND 109272 | LDK378 | 1/17/2013 | 20130117 Acknowledge-Breakthrough Therapy Request | FDA acknowledgement of request for Breakthrough Therapy designation. | Other | |
| IND 109272 | LDK378 | 1/17/2013 | 20130117 Safety Report PHHO2013KR000 7-Day | PHHO2013KR000927 7-Day safety report (PS) | Safety Report | |
| IND 109272 | LDK378 | 1/8/2013 | 20130108 0065 Request for Breakthrough Therapy | Submission provides for Novartis' Request for Breakthrough Therapy Designation. (eCTD-seq0065) | Other | 0065 |
| IND 109272 | LDK378 | 1/7/2013 | 20130107 0062 DSUR 2011-2012 | DSUR report covering the period November 08, 2011 through November 07, 2012. (eCTD-seq0062) | DSUR | 0062 |
| IND 109272 | LDK378 | 12/19/2012 | 20121219 0063 New Investigator CLDK378A2201 | New investigator(s) for study protocol CLDK378A2201 (eCTD-seq0063) | New Investigator | 0063 |
| IND 109272 | LDK378 | 12/18/2012 | 20121218 0064 Safety Report PHHO2012JP016 | PHHO2012JP016929; follow-ip (eCTD-seq 0064) | Safety Report | 0064 |
| IND 109272 | LDK378 | 12/14/2012 | 20121214 0061 CMC Information Amendment | Novartis is submitting an Information Amendment to provide for the following changes Drug Product changes: 2.1.P.2: Addition of an extemporaneous preparation to the Pharmaceutical Development, including stability data and 2.1.P.8: Updated stability data and extension of shelf life to 36 months. (eCTD-eq0061) | CMC Information Amendment | 0061 |
| IND 109272 | LDK378 | 12/10/2012 | 20121210 0059 New Protocol CLDK378X2103 | New protocol for Study CLDK378X2103 entitled "A Phase I, open-label, dose escalation study of LDK378 in pediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)" (eCTD-seq0059) | New Protocol | 0059 |
| IND 109272 | LDK378 | 12/6/2012 | 20121206 0060 Safety Report PHHO2012JP016 | PHHO2012JP016929 follow-up (eCTD-seq0060) | Safety Report | 0060 |
| IND 109272 | LDK378 | 12/5/2012 | 20121205 0058 New Protocol CLDK378A2105 | New Protocol for CLDK378A2105 (eCTD-seq0058) | New Protocol | 0058 |
| IND 109272 | LDK378 | 12/5/2012 | 20121205 HA Mtg Minutes Type B | FDA meeting minutes from the Type B meeting held on November 20, 2012 to seek FDA's advice on the ongoing Phase 1 study (CLDK378X2101), the proposed confirmatory | HA Mtg Minutes | |

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| | | | 20121120 | Phase 3 Study (CLDK378A2303), and the proposed clinical pharmacology program for LDK378. | | |
| IND 109272 | LDK378 | 12/3/2012 | 20121203 0057 Letter of Authorization | Novartis authorizes the FDA to reference IND 109,272 for LDK378, initially submitted on Oct 8, 2010, in support of a single patient IND application by Dr A Shaw, MD. (eCTD-seq0057) | Letter of Authorization | 0057 |
| IND 109272 | LDK378 | 11/30/2012 | 20121130 0056 New Investigator CLDK378A2201 CLDK378A2203 | New Investigator for Protocols CLDK378A2201 and CLDK378A2203. (eCTD-seq0056) | New Investigator | 0056 |
| IND 109272 | LDK378 | 11/29/2012 | 20121129 0053 CMC Information Amendment | CMC amendment provides for changes to the Drug substance and Drug product. (eCTD-seq0053) | CMC Information Amendment | 0053 |
| IND 109272 | LDK378 | 11/20/2012 | 20121120 0054 Letter of Authorization | Novartis authorizes the FDA to reference IND 109,272 for LDK378, initially submitted on October 8, 2010, in support of a single patient IND application by Dr Gail Wagner, MD. (eCTD-seq0054) | Letter of Authorization | 0054 |
| IND 109272 | LDK378 | 11/20/2012 | 20121120 0055 Safety Report PHHO2012DE016 | PHHO2012DE016261 (eCTD-seq0055) | Safety Report | 0055 |
| IND 109272 | LDK378 | 11/14/2012 | 20121114 0052 CMC Information Amendment | Novartis is submitting an CMC Information Amendment to provide for changes to the drug substance and drug product. (eCTD-seq0052) | CMC Information Amendment | 0052 |
| IND 109272 | LDK378 | 11/1/2012 | 20121101 0051 New Investigator CLDK378A2101 | New Investigator(s) for protocol(s) CLDK378A2101 (eCTD-seq 0051) | New Investigator | 0051 |
| IND 109272 | LDK378 | 10/23/2012 | 20121023 0050 Briefing Book Type B EOP2 20121120 | Novartis is providing the Briefing Book for the Type B EOP2 meeting scheduled for November 20, 2012 discuss the clinical development program for LDK378 for non-small cell lung cancer. (eCTD-seq0050) | Briefing Book | 0050 |
| IND 109272 | LDK378 | 10/22/2012 | 20121022 0049 Safety Report PHHO2012DE013 | PHHO2012DE013440; follow-up (eCTD-seq0049) | Safety Report | 0049 |
| IND 109272 | LDK378 | 10/18/2012 | 20121018 Meeting Request Grant Written Response 20121120 Type B | FDA letter granting meeting request for a Type B meeting schedule for November 20, 2012 to seek FDA's advice on the ongoing Phase 1 study (CLDK378X2101), the proposed confirmatory Phase 3 study (CLDK378A2303), and the proposed clinical pharmacology program for LDK378. | Meeting Request Grant Written Response | |
| IND 109272 | LDK378 | 9/28/2012 | 20120928 0047 CMC Information Amendment | Submission of an Information Amendment to provide the changes for the drug substance,drug product and complete summary of changes (eCTD-seq0047). | CMC Information Amendment | 0047 |
| IND 109272 | LDK378 | 9/28/2012 | 20120928 0048 Safety Report PHHO2012DE013 | PHHO2012DE013440 (eCTD-seq0048) | Safety Report | 0048 |
| IND 109272 | LDK378 | 9/27/2012 | 20120927 0046 Request for FDA Mtg Type A | Submission provides request for a Type A meeting to discuss the development of LDK378 as a treatment of adult patients with non-small cell lung cancer characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK). (eCTD-seq0046) | Request for FDA Mtg | 0046 |
| | | | | New Protocol CLDK378A2101, entitled " A randomized, open label, three-treatment, | | |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 9/14/2012 | 20120914 0045 New Protocol CLDK378A2101 | two period cross-over study to determine the relative bioavailability of LDK378 administered either with a low-fat low calorie or high-fat high calorie meal compared to fasted condition in healthy subjects (eCTD-seq0045)." | New Protocol | 0045 |
| IND 109272 | LDK378 | 9/14/2012 | 20120914 0044 New Protocol CLDK378A2201, A2203 | New Protocol CLDK378A2201, entitled "A phase II, multicenter, single-arm study of oral LDK378 in adult patients with ALK-activated non-small cell lung cancer previously treated with chemotherapy and crizotinib" and CLDK378A2203, entitled "A phase II, multicenter, single-arm study of oral LDK378 in crizotinib naïve adult patients with ALK-activated non-small cell lung cancer" (eCTD-seq0044) | New Protocol | 0044 |
| IND 109272 | LDK378 | 8/14/2012 | 20120814 0043 Safety Report PHHO2012US009 | PHHO2012US009809; follow-up (eCTD-seq0043) | Safety Report | 0043 |
| IND 109272 | LDK378 | 8/13/2012 | 20120813 0042 Safety Report PHHO2012BE010 | PHHO2012BE010098; follow-up (eCTD-seq0042) | Safety Report | 0042 |
| IND 109272 | LDK378 | 8/2/2012 | 20120802 0041 Safety Report PHHO2012BE010 | PHHO2012BE010098 (eCTD-seq0041) | Safety Report | 0041 |
| IND 109272 | LDK378 | 7/27/2012 | 20120727 0040 Change in Protocol LDK378X2101 Amendment 3 | Amendment 3 to protocol LDK378X2101 (eCTD-seq0040) | Change in Protocol | 0040 |
| IND 109272 | LDK378 | 7/11/2012 | 20120711 0039 Safety Report PHHO2012US009 | PHHO2012US009809 (eCTD-seq0039) | Safety Report | 0039 |
| IND 109272 | LDK378 | 5/30/2012 | 20120530 0038 Safety Report PHHO2012ES005 | PHHO2012ES005961; follow-up (eCTD-seq0038) | Safety Report | 0038 |
| IND 109272 | LDK378 | 5/30/2012 | 20120530 0037 Safety Report PHHO2012US002 | PHHO2012US002879; follow-up (eCTD-seq0037) | Safety Report | 0037 |
| IND 109272 | LDK378 | 5/24/2012 | 20120524 0036 Safety Report PHHO2012US002 | PHHO2012US002977; follow-up (eCTD-seq0036) | Safety Report | 0036 |
| IND 109272 | LDK378 | 5/18/2012 | 20120518 0035 Response to FDA Request Clinical | Response to FDA request dated May 1, 2012 for clinical information regarding the two dose limiting toxicities at the 600 mg dose cohort level (eCTD-seq0035). | Response to FDA Request | 0035 |
| IND 109272 | LDK378 | 5/18/2012 | 20120518 0035 Response to FDA Request | Response to FDA Request for Information concerning the status of study CLDK378X2101 | Response to FDA Request | 0035 |
| IND 109272 | LDK378 | 5/10/2012 | 20120510 0034 Change in Protocol CLDK378X2101 | Amendment 2 for protocol CLDK378X2101 (eCTD-seq0034) | Change in Protocol | 0034 |
| IND 109272 | LDK378 | 5/10/2012 | 20120510 0033 General Correspondence Change in Regulatory Contact | Correspondence sent to the FDA to inform them that Richard Mountfield is now the regulatory contact (eCTD-seq0033). | General Correspondence | 0033 |
| IND 109272 | LDK378 | 5/2/2012 | 20120502 0032 Safety Report PHHO2012NZ006 | PHHO2012NZ006303; follow-up(eCTD-seq0032) | Safety Report | 0032 |

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|---|---|---|---|---|---|---|
| IND 109272 | LDK378 | 5/1/2012 | 20120501 0031 Safety Report PHHO2012NZ006 | PHHO2012NZ006303 (eCTD-seq0031) | Safety Report | 0031 |
| IND 109272 | LDK378 | 5/1/2012 | 20120501 0030 Safety Report PHHO2012ES005 | PHHO2012ES005961 (eCTD-seq0030) | Safety Report | 0030 |
| IND 109272 | LDK378 | 4/18/2012 | 20120418 0029 New Investigator CLDK378X2101 | New Investigator for protocol CLDK378X2101 (eCTD-seq0029). | New Investigator | 0029 |
| IND 109272 | LDK378 | 4/4/2012 | 20120404 0028 Response to FDA Request Clinical | Response to FDA Request dated December 29, 2011 for notification of two dose limiting toxicities at the 600 mg dose cohort level (eCTD-seq0028). | Response to FDA Request | 0028 |
| IND 109272 | LDK378 | 3/20/2012 | 20120320 0027 Safety Report PHHO2012IT0017 | PHHO2012IT001797; follow-up (eCTD-seq0027) | Safety Report | 0027 |
| IND 109272 | LDK378 | 3/14/2012 | 20120314 0026 Safety Report PHHO2012IT0007 | PHHO2012IT000757; follow-up (eCTD-seq0026) | Safety Report | 0026 |
| IND 109272 | LDK378 | 3/12/2012 | 20120312 0025 Safety Report PHHO2012US002 | PHHO2012US002879; follow-up (eCTD-seq0025) | Safety Report | 0025 |
| IND 109272 | LDK378 | 3/7/2012 | 20120307 0024 Safety Report PHHO2012IT0017 | PHHO2012IT001797; follow-up (eCTD-seq0024) | Safety Report | 0024 |
| IND 109272 | LDK378 | 2/29/2012 | 20120229 0023 Safety Report PHHO2012US002 | PHHO2012US002977; (eCTD-seq0023) | Safety Report | 0023 |
| IND 109272 | LDK378 | 2/28/2012 | 20120228 0022 Safety Report PHHO2012US002 | PHHO2012US002879; (eCTD-seq0022) | Safety Report | 0022 |
| IND 109272 | LDK378 | 2/27/2012 | 20120227 0021 Safety Report PHHO2012IT0017 | PHHO2012IT001797; follow-up (eCTD-seq0021) | Safety Report | 0021 |
| IND 109272 | LDK378 | 2/22/2012 | 20120222 0020 Safety Report PHHO2012IT0017 | PHHO2012IT001797; follow-up (eCTD-seq0020) | Safety Report | 0020 |
| IND 109272 | LDK378 | 2/9/2012 | 20120209 0018 Response to FDA Request 20111229 | Response to request to notify FDA of two DLTs that occurred at the 750 mg dose cohort level in study CLDK378X2101. (eCTD-seq0018) | Response to FDA Request | 0018 |
| IND 109272 | LDK378 | 2/7/2012 | 20120207 0019 Safety Report PHHO2012IT0017 | PHHO2012IT001797 (eCTD-seq0019) | Safety Report | 0019 |
| IND 109272 | LDK378 | 1/23/2012 | 20120123 0017 Safety Report PHHO2012IT0007 | PHHO2012IT000757; (eCTD-seq0017) | Safety Report | 0017 |
| IND 109272 | LDK378 | 1/5/2012 | 20120105 0016 DSUR 2010-2011 | DSUR report covering the period from November 08, 2010 through November 07, 2011(eCTD-seq0016) | DSUR | 0016 |
| IND 109272 | LDK378 | 12/29/2011 | 20111229 Study May Proceed | FDA LETTER stating that protocol CLDK378X2101 may proceed. | Study May Proceed | |
| IND 109272 | LDK378 | 12/1/2011 | 20111201 0015 DSUR eCTD Placement | Correspondence to provide the proposed placement of the DSUR in the eCTD structure (eCTD-seq0015). | Other | 0015 |
| IND 109272 | LDK378 | 10/31/2011 | 20111031 0013 Safety Report PHHO2011ES137 | PHHO2011ES13799; follow-up (eCTD-seq0013) | Safety Report | 0013 |
| IND 109272 | LDK378 | 10/24/2011 | 20111024 0012 DSUR | Request to submit the DSUR in lieu of the annual report using the existing reporting | Other | 0012 |

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|---|---|---|---|---|---|---|
| | | | Harmonization Request | period November 8, 2010 to November 7, 2011. (eCTD-seq0012). | | |
| IND 109272 | LDK378 | 10/17/2011 | 20111017 0011 General Correspondence Study Update | Correspondence to provide an update for the cohort dose level study (eCTD-seq0011). | General Correspondence | 0011 |
| IND 109272 | LDK378 | 9/13/2011 | 20110913 0010 Safety Report PHHO2011ES137 | PHHO2011ES13799; follow-up (eCTD-seq0010) | Safety Report | 0010 |
| IND 109272 | LDK378 | 9/7/2011 | 20110907 0009 Safety Report PHHO2011ES137 | PHHO2011ES13799; follow-up (eCTD-seq0009) | Safety Report | 0009 |
| IND 109272 | LDK378 | 8/24/2011 | 20110824 0008 Safety Report PHHO2011ES137 | PHHO2011ES13799 (eCTD-seq0008) | Safety Report | 0008 |
| IND 109272 | LDK378 | 8/3/2011 | 20110803 0007 Change in Protocol CLDK378X2101 Amendment 01 | Amendment 01 to protocol CLDK378X2101 (eCTD-seq0007). | Change in Protocol | 0007 |
| IND 109272 | LDK378 | 7/19/2011 | 20110719 0006 CMC Information Amendment | CMC Amendment to provide for an additional drug product strength, LDK378 150 mg Hard Gelatin Capsules (eCTD-seq0006) | CMC Information Amendment | 0006 |
| IND 109272 | LDK378 | 7/11/2011 | 20110711 0005 New Investigator CLDK378X2101 | New Investigator for Protocol CLDK378X2101 (eCTD-seq0005) | New Investigator | 0005 |
| IND 109272 | LDK378 | 5/27/2011 | 20110527 0004 New Investigator CLDK378X2101 | New Investigator for Protocol CLDK378X2101 (eCTD-seq0004). | New Investigator | 0004 |
| IND 109272 | LDK378 | 3/15/2011 | 20110315 0003 New Investigator LDK378X2101 | New Investigator for protocol LDK378X2101 (eCTD-seq0003) | New Investigator | 0003 |
| IND 109272 | LDK378 | 1/31/2011 | 20110131 0002 New Investigator CLDK378X2101 | New Investigator for Protocol CLDK378X2101 (eCTD-seq0002) | New Investigator | 0002 |
| IND 109272 | LDK378 | 12/6/2010 | 20101206 Clinical hold | FDA LETTER placing the IND on partial clinical hold. | Clinical hold | |
| IND 109272 | LDK378 | 12/1/2010 | 20101201 0001 Response to FDA Request IND Review | Response to FDA requests from October 29, 2010 through November 8, 2010 for information pertaining to the review of the IND, which were originally sent through email (eCTD-seq0001). | Response to FDA Request | 0001 |
| IND 109272 | LDK378 | 11/8/2010 | 20101108 Email IND 109272 Status | Email from the FDA providing feedback regarding the status of IND 109,272 and the non-hold related comments. | Email | |
| IND 109272 | LDK378 | 11/3/2010 | 20101103 Email Information Deficiencies | Email from the FDA providing a list of clinical deficiencies for the original IND. | Email | |
| IND 109272 | LDK378 | 10/8/2010 | 20101008 0000 Original IND | Original IND for the treatment of tumors characterized by genetic abnormalities in anaplastic lymphoma kinase (ALK) (eCTD-seq0000). | Original IND | 0000 |

US Regulatory Record Indexing Report for NDAs

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|---|---|---|---|---|---|---|
| NDA 205755 | LDK378 | 4/30/2014 | 20140430 Email First PMC | Email correspondence with FDA in regards to the first PMC. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/30/2014 | 20140430 0047 CMC Supplement CBE PMC 2147-7 | Novartis is submitting this CBE0 Supplement to provide for the addition of a method and specification for determination of water to the LDK378 150 mg Hard Gelatin Capsules testing monograph. (eCTD-seq0047) | Changes Being Effected | |
| NDA 205755 | LDK378 | 4/29/2014 | 20140429 Approval letter Accelerated | FDA accelerated approval letter for for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. | Approval letter | --NA-- |
| NDA 205755 | LDK378 | 4/28/2014 | 20140428 Email Linhai Site | Email to FDA regarding information on the Linhai site. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/28/2014 | 20140428 0046 Amendment to pending application Response to FDA Request CMC | Submission provides an amendment to Novartis response document to FDA dated April 17, 2014 in response to question 3 regarding the control and contamination sources Novartis stated that an air shower was used. (eCTD-seq0046) | Amendment to pending application | --NA-- |
| NDA 205755 | LDK378 | 4/24/2014 | 20140424 0045 Response to FDA Request CMC 20140416 Email | Response to CMC information request received in email dated April 16, 2014. (eCTD-seq0045) | Response to FDA Request | |
| NDA 205755 | LDK378 | 4/18/2014 | 20140418 Telecon Linhai Site | Novartis telecon report with FDA regarding the Linhai Site. | Telecon | |
| NDA 205755 | LDK378 | 4/17/2014 | 20140417 Email NVS Response Linhai Site | Email: Novartis response to FDA Questions received 16 April 2014 regarding Zhejiang Jiuzhou Pharmaceutical Co., Linhai site. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/16/2014 | 20140416 Email Telecon Mtg Agenda 20140417 | Email from FDA listing meeting discussion points for telecon scheduled for April 17, 2014. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/16/2014 | 20140416 0044 Response to FDA Request 20140411 CMC | Response to FDA CMC request dated April 11, 2014 regarding Zhejiang Pharmaceuticals - Linhai Site. (eCTD-seq0044) | Response to FDA Request | |
| NDA 205755 | LDK378 | 4/16/2014 | 20140416 Email Telcon Discussion Points | Email from FDA regarding discussion points in preparation for the telecon scheduled for April 17, 2014. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/15/2014 | 20140415 Email Office of Compliance | Novartis email responses to Office of Compliance. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/15/2014 | 20140415 HA Mtg Minutes Late-Cycle | FDA minutes from the Late-Cycle meeting dated March 28, 2014. | HA Mtg Minutes | --NA-- |
| NDA 205755 | LDK378 | 4/11/2014 | 20140411 Email FDA Questions Linhai Site | Email from FDA with additional questions regarding manufacturing of the C1 and C3 intermediates at the Zhejiang Jiuzhou Pharmaceutical Co at the LinHai site. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/10/2014 | 20140410 0043 Amendment to pending application PMRs and PMCs | Novartis is formally submitting a document with the proposed PMRs and PMCs as well as their associated milestone timelines. (eCTD-seq0043) | Amendment to pending application | --NA-- |
| | | | 20140410 0042 | Response to FDA email request #28 dated | | |

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|---|---|---|---|---|---|---|
| NDA 205755 | LDK378 | 4/10/2014 | Response to FDA Request 20140409 Email | April 9, 2014 regarding container label. Also included with submission is the revised labeling. (eCTD-seq0042) | Response to FDA Request | |
| NDA 205755 | LDK378 | 4/9/2014 | 20140409 Email FDA Request Container Label | Email request from FDA regarding the container label. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/8/2014 | 20140408 0039 Revised labeling and Subpart H PMR | Submission provides the revised labeling and Subpart H PMR. (eCTD-seq0039) | Other | |
| NDA 205755 | LDK378 | 4/8/2014 | 20140408 0041 Labeling Supplement Amendment | Submission provides the revised labeling. (eCTD-seq0041) | | |
| NDA 205755 | LDK378 | 4/7/2014 | 20140407 Email Draft ZYKADIA Label | Email from FDA with comments on the draft ZYKADIA labeling. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/7/2014 | 20140407 0040 Response to FDA Request 20140404 Email | Response to FDA email request dated April 4, 2014 regarding proposed PMRs and PMCs. (eCTD-seq0040) | Response to FDA Request | |
| NDA 205755 | LDK378 | 4/4/2014 | 20140404 Email List of Correspondences | Email response to FDA regarding a listing of Novartis/FDA Correspondences related to Zhejiang Jiuzhou Pharmaceutical Co., Ltd,. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/4/2014 | 20140404 Email FDA Request PMR-PMC Submission | Email request from FDA asking for all of the proposed PMR/PMCs are formally submitted to the NDA. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/3/2014 | 20140403 Email FDA Requested Documents | Email to FDA with attached requested documents from telecon. | Email | --NA-- |
| NDA 205755 | LDK378 | 4/3/2014 | 20140403 Telecon Follow-up Linhai Site | Novartis follow-up telecon report with FDA regarding the Linhai Site. | Telecon | |
| NDA 205755 | LDK378 | 4/2/2014 | 20140402 Telecon Linhai Site | Novartis telecon report with FDA regarding the Linhai Site. | Telecon | |
| NDA 205755 | LDK378 | 3/31/2014 | 20140331 Telecon Revised Core Materials | Novartis telecon report regarding a request to submit revised core materials. | Telecon | |
| NDA 205755 | LDK378 | 3/28/2014 | 20140328 0038 Amendment to CMC Supplement | Novartis is submitting revised test methods and specifications for the drug substance and drug product. (eCTD-seq0038) | Amendment to CMC Supplement | --NA-- |
| NDA 205755 | LDK378 | 3/26/2014 | 20140326 0037 Response to FDA Request 12,17 CMC | Response to FDA requests 12 and 17 regarding CMC information. (eCTD-seq0037) | Response to FDA Request | |
| NDA 205755 | LDK378 | 3/26/2014 | 20140326 Email Test Methods and Specifications | Email to FDA regarding updated test methods and specifications for the ceritinib drug substance and drug product. | Email | --NA-- |
| NDA 205755 | LDK378 | 3/21/2014 | 20140321 0036 Response to FDA Request 26,27 | Response to FDA email requests dated March 14, 2014 request 26 and March 17, 2014 request 27. (eCTD-seq0036) | Response to FDA Request | |
| NDA 205755 | LDK378 | 3/19/2014 | 20140319 0034 Proprietary Name Review Request | Novartis is submitting a request for FDA to review the following proposed proprietary names Primary: ZYKADIA and Alternate: RUSCADI. (eCTD-seq0034) | Other | |
| NDA 205755 | LDK378 | 3/19/2014 | 20140319 0033 Withdrawal of Proposed | Novartis is withdrawing the proposed proprietary name ELCERALK™ from NDA | Other | |

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|---|---|---|---|---|---|---|
| | | | Proprietary Name | 205755. (eCTD-seq0033) | | |
| NDA 205755 | LDK378 | 3/19/2014 | 20140319 0035 Response to FDA Request 20140314 Clinical | Response to FDA email request dated March 14, 2014 for Novartis to preform a risk ratio analysis of the incidence of hyperglycemia (glucose greater than 250 mg/dL based on laboratory values) in the following cohorts of patients in study X2101 treated at 750 mg of LDK378. (eCTD-seq0035) | Response to FDA Request | |
| NDA 205755 | LDK378 | 3/19/2014 | 20140319 Advice-Information Request Methods Validation | FDA information request for methods validation matreials. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 3/18/2014 | 20140318 0032 Response to FDA Request 20140313 Clinical | Response to FDA clinical information request dated March 13, 2014 to provide narratives for patients who experienced syncope in Study X2101. (eCTD-seq0032) | Response to FDA Request | |
| NDA 205755 | LDK378 | 3/18/2014 | 20140318 Email NVS Response CMC Request | Novartis email responses to the questions raised in the Information Request received via email on March 17, 2014. | Email | --NA-- |
| NDA 205755 | LDK378 | 3/17/2014 | 20140317 Email NVS Response to DMF Request | Novartis email response to DMF information request and CMC update. | Email | --NA-- |
| NDA 205755 | LDK378 | 3/14/2014 | 20140314 0031 Response to FDA Request 20140307 Request 5 | Response to FDA request 5 dated March 7, 2014 regarding CMC information. (eCTD-seq0031) | Response to FDA Request | |
| NDA 205755 | LDK378 | 3/13/2014 | 20140313 0030 Response to FDA Request 20140307 CMC | Response to FDA email request 22 dated March 7, 2014 regarding quality documentation. (eCTD-seq0030) | Response to FDA Request | |
| NDA 205755 | LDK378 | 3/13/2014 | 20140313 Email Clinical Information Request | Email request from FDA regarding narratives for patients who experienced syncope in Study X2101. | Email | --NA-- |
| NDA 205755 | LDK378 | 3/12/2014 | 20140312 0029 Response to FDA Request 20140228 CMC | Response to FDA email request dated February 28, 2014 regarding CMC information. (eCTD-seq0029) | Response to FDA Request | |
| NDA 205755 | LDK378 | 3/10/2014 | 20140310 0028 Response to FDA Request 18,19,21 | Response to FDA information requests 18, 19 and 21. (eCTD-seq0028) | Response to FDA Request | |
| NDA 205755 | LDK378 | 3/7/2014 | 20140307 Advice-Information Request Quality | FDA information request regarding the quality section of the Original NDA. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 3/7/2014 | 20140307 Advice-Information Request Container Labeling | FDA information request regarding the container labeling. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 3/6/2014 | 20140306 Advice-Information Request Nonclinical-CMC | FDA nonclinical/CMC information request regarding impurity Q5 (123-13). | Advice-Information Request | --NA-- |
| | | | 20140306 | | | |

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|---|---|---|---|---|---|---|
| NDA 205755 | LDK378 | 3/6/2014 | Advice-Information Request Clinical Pharmacology | FDA Clinical Pharmacology request. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 3/4/2014 | 20140304 Email DMF Holder Request | Email response to FDA request regarding DMF holders. | Email | --NA-- |
| NDA 205755 | LDK378 | 3/4/2014 | 20140304 Email Nonclinical CMC Request | Email from FDA with a non-clinical CMC request. | Email | --NA-- |
| NDA 205755 | LDK378 | 3/4/2014 | 20140304 Email Clinical Information Request | Email from FDA with a clinical information request to provide a summary of any cardiac assessments (including the results of echocardiography and ECGs) in patients who experienced edema (particularly lower extremity edema) in study X2101. | Email | --NA-- |
| NDA 205755 | LDK378 | 3/3/2014 | 20140303 0021 General Correspondence Safety Report-Cataract | Novartis is informing the Agency of a previously reported adverse event (AE) of a cataract resulting in surgery that required hospitalization in Study CLDK378X2101 that has since been changed to a serious adverse event (SAE). (eCTD-seq0021) | General Correspondence | |
| NDA 205755 | LDK378 | 3/3/2014 | 20140303 0027 Response to FDA Request 12 and 16 | Response to FDA email requests 12 and 16 dated February 18th and 24th, 2014. (eCTD-seq0027) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/27/2014 | 20140227 Advice-Information Request CMC | FDA information request regarding CMC information. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 2/26/2014 | 20140226 0026 Follow-up to Filing Communication | Submission provides a follow-up to Filing Communication which contains 2 potential review issues. (eCTD-seq0026) | General Correspondence | |
| NDA 205755 | LDK378 | 2/25/2014 | 20140225 Email Proposed OPDP Submission | Email correspondence with FDA in regards to proposed OPDP submission. | Email | --NA-- |
| NDA 205755 | LDK378 | 2/25/2014 | 20140225 0025 Response to FDA Request 7,8,11,14, and 15 Clinical | Response to FDA email request's dated 07-Feb-2014, 11-Feb-2014, 18-Feb-2014, 21-Feb-2014, and 21-Feb-2014 regarding clinical information. (eCTD-seq0025) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/24/2014 | 20140224 0024 Response to FDA Request 20140220 Email | Response to FDA email request dated February 20, 2014 pertaining to the status of ceritinib USAN approval. (eCTD-seq0024) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/24/2014 | 20140224 Advice-Information Request CMC-Microbiology | FDA CMC-Microbiology information request for Novartis to submit a revised specification that reflects the removal of skip lot testing for microbial enumeration studies. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 2/21/2014 | 20140221 0016 Safety and Efficacy Update Part 5 | Novartis is submitting Part 5 of the rolling Safety and Efficacy Update. (eCTD-seq0016) | General Correspondence | |
| NDA 205755 | LDK378 | 2/21/2014 | 20140221 Email Clinical Information Request X2101 | FDA Clinical information request regarding on-treatment deaths in study X2101. | Email | --NA-- |
| NDA 205755 | LDK378 | 2/21/2014 | 20140221 Email Clinical Information Request AE's | FDA Clinical information request email regarding AE's. | Email | --NA-- |

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|---|---|---|---|---|---|---|
| NDA 205755 | LDK378 | 2/21/2014 | 20140221 Filing Communication Issues Identified | FDA letter notifying Novartis that FDA has completed their filing review and have determined that the application is sufficiently complete to permit a substantive review. | Filing Communication | --NA-- |
| NDA 205755 | LDK378 | 2/20/2014 | 20140220 0022 Response to FDA Request 20140214 Email | Response to FDA Information Request 10 Received February 14, 2014. (eCTD-seq0022) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/20/2014 | 20140220 0023 Response to FDA Request 20140218 Email | Response to FDA email Request No. 11 - part 1a (CP - dataset + define) dated February 18, 2014. (eCTD-seq0023) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/20/2014 | 20140220 Email FDA Request Ceritinib | Email request from FDA regarding ceritinib as an approved USAN name. | Email | --NA-- |
| NDA 205755 | LDK378 | 2/19/2014 | 20140219 0018 Response to FDA Request 20140122 Email | Response to FDA CMC microbiology email request dated January 22, 2014. (eCTD-seq0018) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/19/2014 | 20140219 0015 Safety and Efficacy Update Part 4 | Novartis is submitting Part 4 of the rolling Safety and Efficacy Update. (eCTD-seq0015) | General Correspondence | |
| NDA 205755 | LDK378 | 2/19/2014 | 20140219 0020 Response to FDA Request 20140218 Email | Response to FDA clinical pharmacology information email request dated February 18, 2014. (eCTD-seq0020) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/18/2014 | 20140218 0019 Response to FDA Request 20140211 Email | Response to FDA email request dated February 11, 2014 in which FDA requested that Novartis: 1. Perform an assessment of the association between the use of ceritinib and acute pancreatitis 2. Provide narratives for 3 patients who experienced convulsions 3. Provide a dataset for patients in Study CLDK378X2101 who rogressed on ceritinib with CNS as the primary site of relapse. (eCTD-seq0019) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/18/2014 | 20140218 Advice-Information Request Clinical Pharmacology | FDA Clinical Pharmacology Information Request. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 2/18/2014 | 20140218 Advice-Information Request Biopharmaceutic | FDA Biopharmaceuticals Information Request. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 2/17/2014 | 20140217 0017 Response to FDA Request 20140213 Email | Response to FDA email request dated February 13, 2014 requesting clarification on dataset [arskdth] and an explanation of the values for the [BORRSN] variable. (eCTD-seq0017) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/14/2014 | 20140214 0014 Safety and Efficacy Update Part 3 | Novartis is submitting Part 3 of the rolling Safety and Efficacy Update SCE addendum and associated appendix. (eCTD-seq0014) | General Correspondence | |
| NDA 205755 | LDK378 | 2/14/2014 | 20140214 0013 Response to FDA Request 20140207 Email | Response to FDA email request dated February 7, 2014 in which FDA requested additional exposure-response evidence to support the proposed dosing regimen for ceritinib. (eCTD-seq0013) | Response to FDA Request | |
| | | | 20140214 Email | | | |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
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| NDA 205755 | LDK378 | 2/14/2014 | Clinical Information Request 10 | Email: FDA Clinical information request 10. | Email | --NA-- |
| NDA 205755 | LDK378 | 2/13/2014 | 20140213 Email Clinical Information Request 9 | Email: FDA Clinical Information Request 9 regarding the values for the [BORRSN] variable. | Email | --NA-- |
| NDA 205755 | LDK378 | 2/11/2014 | 20140211 Advice-Information Request Clinical | FDA Clinical information request 8. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 2/10/2014 | 20140210 0011 Response to FDA Request 20140205 Email | Response to FDA email request dated February 5, 2014 regarding the clinical datasets. (eCTD-seq0011) | Response to FDA Request | |
| NDA 205755 | LDK378 | 2/10/2014 | 20140210 0010 General Correspondence Raw Datasets | Submission of raw datasets (31-Oct-2013 cut-off date). (eCTD-seq0010) | General Correspondence | |
| NDA 205755 | LDK378 | 2/7/2014 | 20140207 Advice-Information Request Clinical Pharmacology | FDA Clinical Pharmacology information request for Novartis to conduct a exposure-response analyses using the current datasets for safety, efficacy, and exposure. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 2/6/2014 | 20140206 0009 Request for Proprietary Name | Novartis is submitting a request for FDA to review the proposed proprietary names: Primary: ELCERALK, Alternate 1: ZYKADIA, Alternate 2: RUSCADI. (eCTD-seq0009) | Other | |
| NDA 205755 | LDK378 | 2/5/2014 | 20140205 0008 General Correspondence Safety Data | Novartis is notifying the Agency of 8 serious adverse events (SAEs) and 112 non-serious adverse events (AEs) that were omitted from the clinical database at the time of the ceritinib NDA submission. (eCTD-seq0008) | General Correspondence | |
| NDA 205755 | LDK378 | 2/5/2014 | 20140205 Advice-Information Request Clinical | FDA Clinical information request regarding Novartis amendment dated February 5, 2014 containing communication on the omissions to the NDA 205755 safety database. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 2/3/2014 | 20140203 0007 Response to FDA Request 20140129 Email | Response to FDA email request dated January 29, 2014 asking Novartis to format the datasets to the current version of CDISC/Study Data Tabulation Model (SDTM) version 1.1, SDTM Implementation Guide (SDTMIG) version 3.1.1. (eCTD-seq0007) | Response to FDA Request | |
| NDA 205755 | LDK378 | 1/29/2014 | 20140129 0006 Withdrawal of Proposed Proprietary Name | Novartis is withdrawing the proposed proprietary name CERALK™ from NDA 205755. (eCTD-seq0006) | General Correspondence | |
| NDA 205755 | LDK378 | 1/29/2014 | 20140129 0005 Response to FDA Request 20140122 Email | Response to FDA email request dated January 22, 2014 amendment to the Financial Disclosure Certification. (eCTD-seq0005) | Response to FDA Request | |
| NDA 205755 | LDK378 | 1/29/2014 | 20140129 Advice-Information Request Clinical | FDA Clinical information request regarding study LDK378X2101. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 1/29/2014 | 20140129 HA Mtg Minutes 20140127 | FDA minutes from the January 27, 2014 teleconference to notify the applicant of our concerns with their proposed proprietary name, Ceralk. | HA Mtg Minutes | --NA-- |
| | | | | Response to FDA email request dated | | |

| Application/ Registration Number | Product Code | Submission Date | Submission Folder Name | Content Summary | Submission Type Description | Serial/ Supplement Number |
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| NDA 205755 | LDK378 | 1/24/2014 | 20140124 0004 Response to FDA Request 20140117 Email | January 17, 2014 to submit a study report for the PBPK simulations using SimCYP software to predict the effect of ketoconazole and rifampin on the pharmacokinetics of ceritinib after multiple dosing. (eCTD-seq0004) | Response to FDA Request | |
| NDA 205755 | LDK378 | 1/22/2014 | 20140122 Advice-Information Request CMC | FDA CMC Microbiology information request regarding Novartis proposal to perform skip lot testing for the Microbial Limits test for drug product release. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 1/22/2014 | 20140122 Advice-Information Request Clinical | FDA clinical information request regarding the Financial Disclosure Certification. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 1/17/2014 | 20140117 Advice-Information Request Clinical | FDA clinical request for Novartis to submit a study report for PBPK simulations using SimCYP software to predict the effect of ketoconazole and rifampin on the pharmacokinetics (PK) of ceritinib after multiple dosing [reference studies LDK378A2104 and LDK378A2106]. | Advice-Information Request | --NA-- |
| NDA 205755 | LDK378 | 1/17/2014 | 20140117 Email Coding Question | Email question from FDA regarding the correct coding for AEVNAM3A (EDC). | Email | --NA-- |
| NDA 205755 | LDK378 | 1/14/2014 | 20140114 Email Safety and Efficacy Update | Email regarding the safety and efficacy update. | Email | --NA-- |
| NDA 205755 | LDK378 | 1/9/2014 | 20140109 Email Perceptives Question | Email question from FDA regarding the name and contact information for the regulatory point of contact for Precision Informatics. | Email | --NA-- |
| NDA 205755 | LDK378 | 1/8/2014 | 20140108 0003 Response to FDA Request 20140103 Email | Response to FDA email request dated January 1, 2014 in which Novartis was asked to fill out a 'clinical pharmacology form'. (eCTD-seq0003) | Response to FDA Request | |
| NDA 205755 | LDK378 | 1/6/2014 | 20140106 Acknowledge application Presubmission Part 3 | FDA acknowledgement letter for NDA presubmission dated December 24, 2013. | Acknowledge application | --NA-- |
| NDA 205755 | LDK378 | 1/3/2014 | 20140103 Email Clinical Request Pharmacology Form | Email request from FDA for Novartis to fill out a clinical pharmacology form. | Email | --NA-- |
| NDA 205755 | LDK378 | 12/24/2013 | 20131224 0002 Original NDA Presubmission Part 3 | Novartis submitting an original NDA for CERALK (ceritinib, LDK378) 150 mg capsules for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received prior treatment with an anaplastic lymphoma kinase (ALK) inhibitor. Submission also provides Study CLDK378X2101. (eCTD-seq0002) | Original NDA | |
| NDA 205755 | LDK378 | 12/20/2013 | 20131220 Acknowledge application Presubmission Part 2 | FDA acknowledgement letter for NDA presubmission dated December 12, 2013. | Acknowledge application | --NA-- |
| NDA 205755 | LDK378 | 12/12/2013 | 20131212 0001 Presubmission Part 2 | Novartis is submitting part 2 of the rolling NDA for CERALK™ (ceritinib, LDK378) 150 mg capsules for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received prior treatment with an anaplastic | Other | |

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| | | | | lymphoma kinase (ALK) inhibitor. (eCTD-seq0001) | | |
| NDA 205755 | LDK378 | 12/11/2013 | 20131211 Acknowledge application Presubmission Part 1 | FDA acknowledgement letter for NDA presubmission dated November 27, 2013. | Acknowledge application | --NA-- |
| NDA 205755 | LDK378 | 11/27/2013 | 20131127 0000 Presubmission Part 1 | Novartis is submitting part 1 of the rolling NDA for CERALK™ (LDK378) 150 mg capsules for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who have received prior treatment with an anaplastic lymphoma kinase (ALK) inhibitor. (eCTD-seq0000) | Other | |