Docket No.: PRD2200USDIV1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 8,344,011
Inventors:	Henry J. Breslin, Chaozhong Cai, Wei He, and Robert W. Kavash
Assignee:	Janssen Pharmaceutica, N.V.
Title:	Compounds as opioid receptor modulators
Issue Date:	January 1, 2013

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

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

Dear Madam:

Janssen Pharmaceutica, N.V. ("Janssen") hereby requests an extension of the term of U.S. Patent No. 8,344,011 ("the '011 Patent", Exhibit 1) of 606 days pursuant to 35 U.S.C. §156. This request is based on the first approval for commercial marketing or use of the drug product VIBERZI™ (eluxadoline). The marketing authorization for VIBERZI™ is held by Forest Tosara Limited ("Forest Tosara"). Forest Tosara consents to this application for patent term extension as shown by the Consent of NDA Holder submitted herewith (Exhibit 2).

Janssen Pharmaceutica, N.V. ("Janssen") is the owner of the '011 Patent by assignment. The '011 Patent was assigned by the inventors to Janssen on May 4, 2005 and May 5, 2005 (recorded at Reel 32671, Frame 648 on April 15, 2014) (Exhibit 3).

As permitted by 37 C.F.R. §1.785 and MPEP §2761, Janssen is concurrently filing requests for patent term extensions of U.S. Patent Nos. 7,741,356 and 8,609,709 based upon the same regulatory review period.

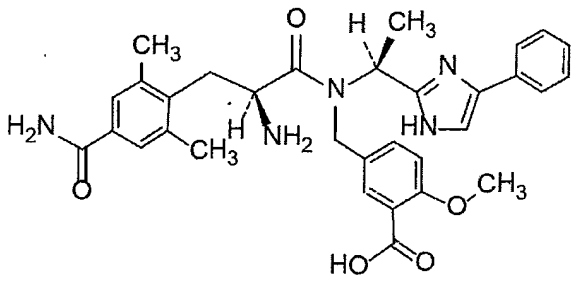
The following information is submitted in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.740, and follows the numerical format set forth in 37 C.F.R. §1.740(a):

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

The approved product is VIBERZI™ (eluxadoline) 75 and 100 mg tablets for oral administration. Eluxadoline has:

(1) the chemical name of 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6-dimethylphenyl] 1-oxopropyl][(1S)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid;

(2) the structural formula of:



(3) the empirical formula of $C_{32}H_{35}N_5O_5$, and

(4) a molecular weight of 569.65.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.

The regulatory review of VIBERZI™ occurred under an Investigational New Drug (IND) application and a New Drug Application (NDA) pursuant to sections 505(i) and (b) of the Federal Food, Drug and Cosmetic Act (FFDCA), respectively, which are codified at 21 U.S.C. §355(i) and (b).

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

On May 27, 2015, the FDA issued an "approval letter" (Exhibit 4) for the new drug application (NDA No. 206940) for VIBERZI™ (eluxadoline). Although FDA takes the position that the approval is effective on the date of the approval letter (p. 2 of Exhibit 4), Applicant questions whether "the product received permission for commercial marketing" on that date within the meaning of 35 U.S.C. §156. Under the terms of the approval letter, Forest Tosara cannot market VIBERZI™ until the Drug Enforcement Administration (DEA) has made a final scheduling decision, i.e., listed VIBERZI™ on the Schedule of Controlled Substances under 21 U.S.C. §823. Exhibit 4, p. 1. Nonetheless, in order to avoid potential forfeiture of a patent term extension for the '011 Patent under 35 U.S.C. §156(d)(1) based on FDA's current position, Janssen submits this

application within 60 days of the May 27, 2015 approval letter. In so doing, Janssen does not waive its right to challenge FDA's position that VIBERZI™ was approved, or that the product received permission for commercial marketing within the meaning of 35 U.S.C. §156, as of the date of the approval letter.

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

VIBERZI™ is a human drug product, the sole active ingredient of which is eluxadoline. VIBERZI™ is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

Neither eluxadoline nor any salt or ester of it has 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 letter referenced herein on May 27, 2015.

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

An approval letter for VIBERZI™ was mailed by FDA on May 27, 2015. The sixty day period (assuming it begins on the date of the approval letter) expires on Monday, July 27, 2015. (The 60th day is Sunday, July 26, 2015. Pursuant to 37 C.F.R. §1.7 and MPEP §2753, the last day on which the application can be submitted is the next business day.) The present application, therefore, is timely filed within the sixty day period.

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

Inventors:	Henry J. Breslin, Chaozhong Cai, Wei He, and Robert W. Kavash
Assignee:	Janssen Pharmaceutica, N.V.
U.S. Patent No.:	8,344,011
U.S. Serial No.:	12/838,825
Issue Date:	January 1, 2013
Expiration Date:	March 14, 2025

The 20 year term of the '011 Patent pursuant to 35 U.S.C. §154(a)(2) expires March 14, 2025.

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

A copy of U.S. Patent No. 8,344,011, the patent for which an extension is being sought, is attached as Exhibit 1.

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

No disclaimers, certificates of correction or reexamination certificates have been submitted or issued for the '011 Patent.

No maintenance fees are yet due in connection with the '011 Patent.

(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.

The '011 Patent claims a method of using the approved product. In particular, at least claims 1, 2, 5-33, 46, 48-52, 63, 65, and 77 of the '011 Patent read on a method of using the approved product. For example, claim 65 recites:

65. A method for treating or pain or gastrointestinal disorder, wherein said pain is centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, pain related to inflammation, progressive disease related pain, neuropathic pain, acute pain, or chronic pain, and wherein said gastrointestinal disorder is ulcerative colitis, Crohn's disease, diarrhea-predominant irritable bowel syndrome, or alternating irritable bowel syndrome in a subject in need thereof comprising administering to the subject a therapeutically effective amount of 5-({[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid or a pharmaceutically acceptable enantiomer, diastereomer, racemate, or salt thereof.

Viberzi, which is the S,S-diastereomer of 5-({[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid, is approved for treatment of irritable bowel syndrome with diarrhea (IBS-D).

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

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

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

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

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

The investigational new drug (IND) application for VIBERZI™ (eluxadoline) was submitted on November 21, 2007 by Johnson & Johnson Pharmaceutical Research & Development LLC ("J&J R&D") (Exhibit 5). The IND number assigned was 79,214. IND No. 79,214 became effective on December 21, 2007 pursuant to 21 U.S.C. §355(i)(2). The IND was transferred from J&J R&D to PPD Therapeutics Inc. on December 2, 2009 (Exhibits 6 and 7). The FDA acknowledged the change in the sponsor of the IND on December 11, 2009 (Exhibit 8). PPD Therapeutics Inc. subsequently changed its name to Furiex Pharmaceuticals, Inc. ("Furiex"), which was acknowledged by FDA on March 30, 2010 (Exhibit 9).

A new drug application (NDA) for VIBERZI™ (eluxadoline) was submitted by Furiex on June 26, 2014 (Exhibit 11). The NDA was assigned NDA No. 206940.

An approval letter for NDA No. 206940 for VIBERZI™ was mailed on May 27, 2015 (Exhibit 4). Furiex transferred the NDA to Forest Tosara Limited on July 16, 2015 (Exhibit 13).

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

IND No. 79,214 for VIBERZI™ (eluxadoline) was submitted on November 21, 2007 by J&J R&D (Exhibit 5). IND No. 79,214 became effective on December 21, 2007 pursuant to 21 U.S.C. §355(i)(2). The IND was transferred from J&J R&D to PPD Therapeutics Inc. on December 2, 2009 (Exhibits 6 and 7). The FDA acknowledged the change in the sponsor of the IND on December 11, 2009 (Exhibit 8). PPD Therapeutics Inc. subsequently changed its name to Furiex, which was acknowledged by FDA on March 30, 2010 (Exhibit 9). A list of the correspondence between J&J R&D, PPD Therapeutics Inc., and Furiex and FDA during the IND phase is provided in Exhibit 10.

The NDA for VIBERZI™ (NDA No. 206940) was submitted by Furiex on June 26, 2014 (Exhibit 11). A list of the correspondence between Furiex and FDA during the NDA phase is provided in Exhibit 12.

An approval letter for VIBERZI™ was mailed on May 27, 2015 (Exhibit 4). Furiex transferred the NDA to Forest Tosara Limited on July 16, 2015 (Exhibit 13).

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

Statement of Eligibility of the Patent for Extension under 35 U.S.C. §156

It is the opinion of the applicant that the '011 Patent is eligible for a patent term extension under 35 U.S.C. §156 and 37 C.F.R. §1.720 because it satisfies all of the requirements for such an extension as follows:

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

The '011 Patent claims a method of using an approved human drug product, eluxadoline.

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

The term of the '011 Patent has not expired before the submission of this application as its expiration date is March 14, 2025.

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

The term of the '011 Patent 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)

This application is submitted by Janssen, the owner of the '011 Patent, in accordance with 35 U.S.C. §156(d) and 37 C.F.R. §1.740. Forest Tosara, the holder of the NDA for VIBERZI™, has consented to this application for patent term extension (Exhibit 2). The application has been submitted within the sixty-day period (assuming the period begins on the date of the May 27, 2015 approval letter) and contains the information required under 35 U.S.C. §156(d)(1).

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

The approved product was the subject of an IND, which became effective on December 21, 2007, and an NDA filed on June 26, 2014 and approved on May 27, 2015. Thus, the product was subject to a regulatory review period under §505(b) of the FFDCA before its commercial marketing or use.

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

The permission for the commercial marketing of the product VIBERZI™ is the first received permission for commercial marketing or use under FFDCA §505 under which the regulatory review occurred. This is evidenced by the absence of any approved NDA under which VIBERZI™ or eluxadoline could be commercially marketed or used prior to the May 27, 2015 approval letter for VIBERZI™.

G. 35 U.S.C. §156(c)(4) and 37 C.F.R. §1.720(h)

No other patent term has been extended for the same regulatory review period for the product VIBERZI™.

H. 35 U.S.C. §156(d)(1) and 37 C.F.R. §1.720(f)

This application is submitted within the sixty-day period beginning May 27, 2015 (assuming the period begins on the date of the May 27, 2015 approval letter). The patent owner, Janssen, submits this patent term extension application with the consent of Forest Tosara, the NDA holder (Exhibit 2).

Statement as to the Length of the Extension Claimed

in Accordance with 37 C.F.R. §1.775

The applicant claims an extension of 606 days. The length of the extension was calculated as shown below.

(1)	2379	The number of days in: the period beginning on the effective date of the IND (December 21, 2007) and ending on the date the NDA was initially submitted (June 26, 2014). This is the "testing phase" as defined in 37 C.F.R. §1.775(c)(1).
(2)	335	The number of days in the period beginning on the date the NDA was initially submitted (June 26, 2014) and ending on the date of NDA approval (May 27, 2015). This is the "approval phase" as defined in 37 C.F.R. §1.775(c)(2).
(3)	2714	The sum of (1) and (2). This is the regulatory review period as defined in 37 C.F.R. §1.775(c).
(4)	0	The number of days in the approval phase (2) which were on and before issuance of the '011 Patent. 37 C.F.R. §1.775(d)(1)(i).
(5)	0	The number of days in the approval phase (2) during which the Applicant did not act with due diligence. 37 C.F.R. §1.775(d)(1)(ii).
(6)	0	The sum of (4) and (5).
(7)	2714	The difference between the regulatory review period (3) and (6). 37 C.F.R. §1.775(d)(1)(ii).
(8)	1838	The number of days of the period of the testing phase (1) which occurred prior to the issuance of the '011 Patent. 37 C.F.R. §1.775(d)(1)(i).
(9)	0	The number of days of the period of the testing phase (1) during which the Applicant failed to act with due diligence 37 C.F.R. §1.775(d)(1)(ii).

(10)	1838	The sum of (8) and (9).
(11)	876	The difference between the regulatory review period (7) and (10).
(12)	2379	The number of days of the testing phase (1).
(13)	1838	The number of days from (10).
(14)	541	Subtract line (13) from line (12).
(15)	270	One half of (14) 37 C.F.R. § 1.775(d)(1)(iii).
(16)	606	Subtract line (15) from line (11).
(17)	Mar. 14, 2025	The original expiration date of the '011 Patent.
(18)	Nov. 10, 2026	The expiration date of the '011 Patent if the original expiration date is extended by the number of days in line (16). 37 C.F.R. §1.775(d)(2)
(19)	May 27, 2015	The date of approval of the application under § 505(b) of the FFDCA.
(20)	14 years	The limitation of 37 C.F.R. §1.775(d)(3).
(21)	May 27, 2029	The number of years in (20) plus the date on (19). 37 C.F.R. §1.775(d)(3).
(22)	Nov. 10, 2026	The earlier of line (18) or line (21).
(23)	Mar. 14, 2025	The original expiration date of the '011 Patent.
(24)	5 years	The applicable limitation of 37 C.F.R. §1.775(d)(5).
(25)	Mar. 14, 2030	The number of years on (24) plus the date on (23).
(26)	Nov. 10, 2026	The earlier of line (22) or line (25).
(27)	Mar. 14, 2025	The original expiration date of the '011 Patent.
(28)	606	The number of days which is the difference between the date on line (27) and the date on line (26)

(13) A statement that the Applicant acknowledges a duty to disclose to the Commission of Patents and Trademarks and to the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought for the '011 Patent by this application for patent term extension as required by 37 C.F.R. §1.765.

(14) Prescribed Fee

Submitted herewith is the fee required under 37 C.F.R. §1.20(j) of $1,120 for this application. The Commissioner is authorized and requested to charge any deficiency in this fee and any additional fees due with this Application for Extension of Patent Term to Deposit Account No. 100750.

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

Bernard F. Plantz

Johnson & Johnson

One Johnson & Johnson Plaza

New Brunswick, NJ 08933

Attn: Sean C. Brock

Office: (732) 524-6656

Fax: (732) 524-5008

This patent term extension application, including its attachments and supporting papers, is being submitted with two additional copies thereof (for a total of three copies) in accordance with 37 C.F.R. §1.740(b).

In view of the foregoing, Janssen requests that the Commissioner grant an extension of 606 days to U.S. Patent No. 8,344,011.

Favorable action is earnestly solicited.

Dated: July 23, 2015

Respectfully submitted,

By Hal Brent Woodrow
Hal Brent Woodrow
Registration No.: 32,501
Correspondence Customer Number: 45511
Attorney for Applicant

Exhibit List

Exhibit No.	Description
1	U.S. Patent No. 8,344,011
2	Consent of NDA Holder
3	Copy of assignment from inventors to Janssen Pharmaceutica N.V.
4	May 27, 2015 Approval Letter for VIBERZI™
5	November 21, 2007 IND submission letter (IND No. 79,214)
6	December 2, 2009 letter from Johnson & Johnson Pharmaceutical Research & Development LLC regarding change of sponsor to PPD Therapeutics Inc.
7	December 2, 2009 letter from PPD Therapeutics Inc. regarding change of sponsor
8	December 11, 2009 letter from FDA acknowledging change of sponsor to PPD Therapeutics Inc.
9	March 30, 2010 FDA letter acknowledging change of name of PPD Therapeutics Inc. to Furiex Pharmaceuticals, Inc.
10	IND regulatory submission and correspondence chronology log (IND No. 79,214)
11	June 26, 2014 NDA submission letter
12	NDA regulatory submission and correspondence chronology log (NDA No. 206940)
13	July 16, 2015 letters from Furiex Pharmaceuticals, Inc. and Forest Tosara Limited transferring ownership of NDA No. 206940 and IND No. 79,214 to Forest Tosara Limited

Exhibit 1

US008344011B2

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

(10) **Patent No.: US 8,344,011 B2**
(45) **Date of Patent: Jan. 1, 2013**

(54) **COMPOUNDS AS OPIOID RECEPTOR MODULATORS**

(75) Inventors: **Henry J. Breslin**, Lansdale, PA (US); **Chaozhong Cai**, North Wales, PA (US); **Wei He**, Audubon, PA (US); **Robert W. Kavash**, Glenside, PA (US)

(73) Assignee: **Janssen Pharmaceutica, N.V.**, Beerse (BE)

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

(21) Appl. No.: **12/838,825**

(22) Filed: **Jul. 19, 2010**

(65) **Prior Publication Data**

US 2010/0324051 A1 Dec. 23, 2010

Related U.S. Application Data

(60) Division of application No. 11/877,747, filed on Oct. 24, 2007, now Pat. No. 7,786,158, which is a continuation of application No. 11/079,647, filed on Mar. 14, 2005, now Pat. No. 7,741,356.

(60) Provisional application No. 60/553,342, filed on Mar. 15, 2004.

(51) **Int. Cl.**

A61K 31/4174	(2006.01)
A61K 31/4178	(2006.01)
C07D 233/64	(2006.01)

(52) **U.S. Cl.** **514/396**; 514/397; 548/335.5

(58) **Field of Classification Search** 514/396, 514/397; 548/335.5

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,013,658	A	1/2000	Lau et al.
7,282,507	B2	10/2007	Lanter et al.
7,741,356	B2	6/2010	Breslin et al.
7,786,158	B2	8/2010	Breslin et al.

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Callahan "Irritable Bowel Syndrome Neuropharmacology: A Review of Approved and Investigational Compounds" Journal of Clinical Gastroenterology, 2002, vol. 35, pp. 558-567.*

Dufour E, et al; "Synthesis of amidrazones using an engineered papain nitrile hydratase", Elsevier Science Publishers, Amsterdam, NL, vol. 433, No. 1-2, Aug. 14, 1998, pp. 78-82.

Hipskind P, et al "3-Aryl-1,2-diacetamidopropane Derivatives as Novel and Potent NK-1 Receptor Antagonists", Belstein Institute for Organic Chemistry, Frankfurt-Main, DE; XP002330617, Database accession No. BRN: 7491912 abstract, J. Med. Chem., vol. 39, No. 3, 1996, pp. 736-748.

Tam J, et al, "Design and Synthesis of a Multi-Detachable Benzhydrylamine-Resin for Solid Phase Peptide Synthesis", Frankfurt-Main, DE; XP002330618, Database accession No. BRN: 5166497 abstract, Tetrahedron Lett., vol. 22, No. 30, 1981, pp. 2851-2854.

Santi, D, "Tyrosyl Transfer Ribonucleic Acid Synthetase from *Escherichia coli* B. Analysis of Tyrosine and Adenosine 5-Triphospate Binding Sites", Belstein Institute for Organic Chemistry,, Frankfurt-Main, DE; XP002330619, Database accession No. BRN: 7278453 abstract, J. Med. Chem., vol. 16, No. 3, 1973, pp. 273-280.

Search report for International Appl. No. PCT/US2005/008339.

European Patent Application No. EP 10182349: Partial European Search Report dated Feb. 17, 2011, 8 pages.

* cited by examiner

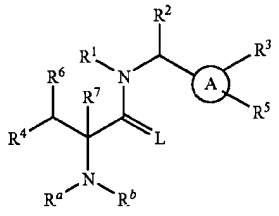
Primary Examiner — Joseph Kosack

(74) *Attorney, Agent, or Firm* — Woodcock Washburn LLP

(57) **ABSTRACT**

The present invention is directed to novel opioid receptor modulators of Formula (I).

Formula (I)



The invention further relates to methods for preparing such compounds, pharmaceutical compositions containing them, and their use in the treatment of disorders that may be ameliorated or treated by the modulation of opioid receptors.

78 Claims, 3 Drawing Sheets

Figure 1

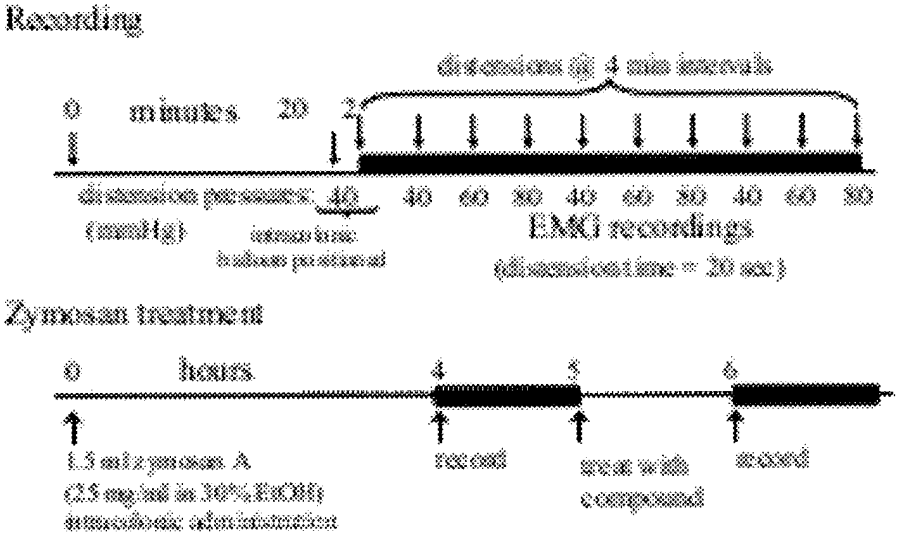

Recording
minutes
20
40
40
60
80
40
60
80
40
60
80
EMG recordings
Zymosan treatment
hours
4
5
6
record
record

Figure 2.

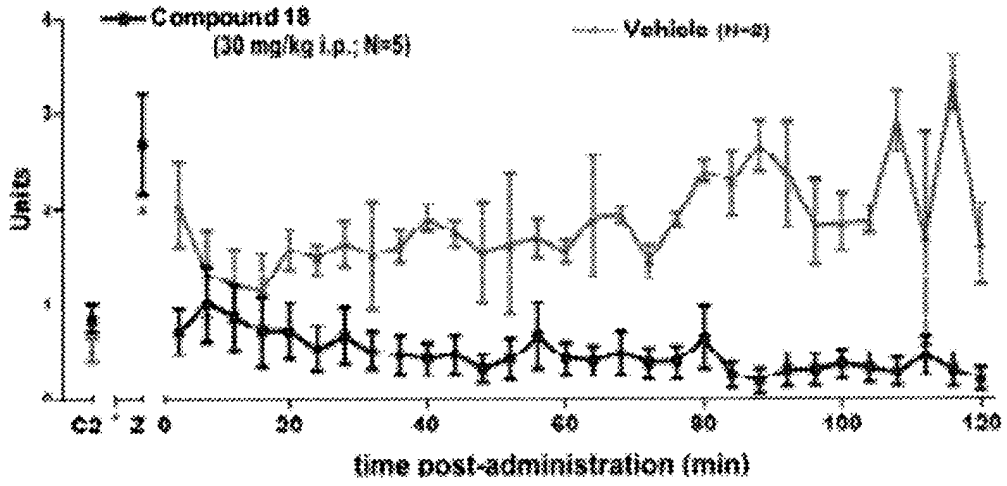
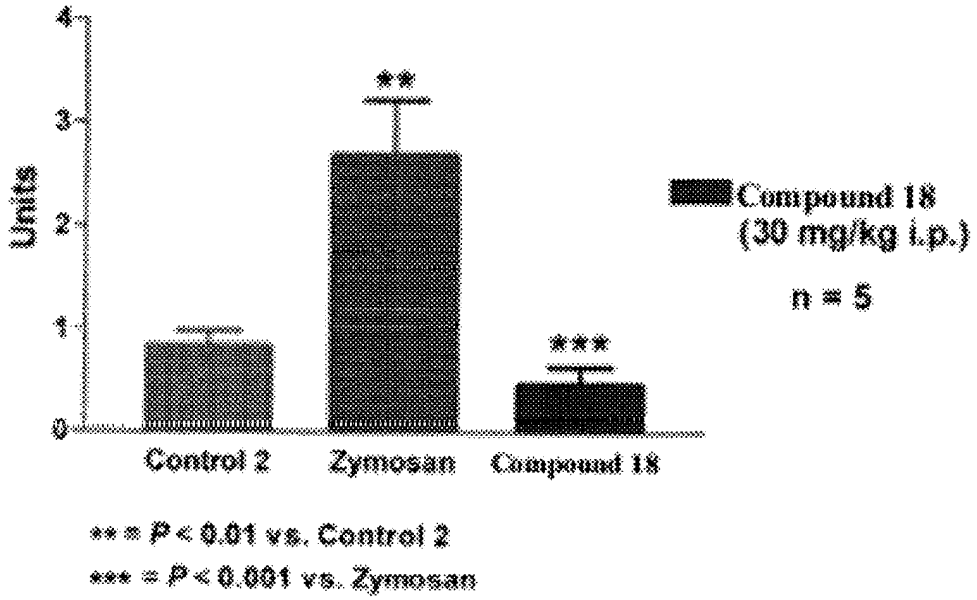

Compound 18
(30 mg/kg i.p.; N=5)
Vehicle (n=5)
Units
time post-administration (min)

Figure 3.


Units
4
3
2
1
0
**
***
Control 2
Zymosan
Compound 18
Compound 18
(30 mg/kg i.p.)
n = 5
** = P < 0.01 vs. Control 2
*** = P < 0.001 vs. Zymosan

COMPOUNDS AS OPIOID RECEPTOR MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

This patent application is a divisional application of patent application Ser. No. 11/877,747, filed on Oct. 24, 2007, currently pending, which was a continuation of patent application Ser. No. 11/079,647, filed on Mar. 14, 2005, issued as U.S. Pat. No. 7,741,356 and claims priority to U.S. Provisional Patent Application 60/553,342, filed on Mar. 15, 2004, now abandoned, each of which is hereby incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

The research and development of the invention described below was not federally sponsored.

FIELD OF THE INVENTION

The present invention is directed to novel opioid receptor modulators of Formula (I). The invention further relates to methods for preparing such compounds, pharmaceutical compositions containing them, and their use in the treatment of opioid modulated disorders.

BACKGROUND OF THE INVENTION

The opioid receptors were identified in the mid-1970's, and were quickly categorized into three sub-sets of receptors (mu, delta and kappa). More recently the original three types of receptors have been further divided into sub-types. Also known is that the family of opioid receptors are members of the G-protein coupled receptor (GPCR) super-family. More physiologically pertinent are the well established facts that opioid receptors are found throughout the central and peripheral nervous system of many mammalian species, including humans, and that modulation of the respective receptors can elicit numerous, albeit different, biological effects, both desirable and undesirable (D. S. Fries, "Analgesics", in *Principles of Medicinal Chemistry,* 4th ed.; W. O. Foye, T. L. Lemke, and D. A. Williams, Eds.; Williams and Wilkins: Baltimore, Md., 1995; pp. 247-269; J. V. Aldrich, "Analgesics", *Burger's Medicinal Chemistry and Drug Discovery,* 5th Edition, Volume 3: Therapeutic Agents, John Wiley & Sons, Inc., 1996, pp. 321-441). In the most current literature, the likelihood of heterodimerization of the sub-classes of opioid receptors has been reported, with respective physiological responses yet undetermined (Pierre J. M. Riviere and Jean-Louis Junien, "Opioid receptors: Targets for new gastrointestinal drug development", Drug Development 2000, pp. 203-238).

A couple biological effects identified for opioid modulators have led to many useful medicinal agents. Most significant are the many centrally acting mu opioid agonist modulators marketed as analgesic agents to attenuate pain (e.g., morphine), as well as peripherally acting mu agonists to regulate motility (e.g., loperamide). Currently, clinical studies are continuing to evaluate medicinal utility of selective delta, mu, and kappa modulators, as well as compounds possessing combined sub-type modulation. It is envisioned such explorations may lead to agents with new utilities, or agents with minimized adverse side effects relative to currently available agents (examples of side effects for morphine includes constipation, respiratory depression, and addiction potential). Some new GI areas where selective or mixed opioid modulators are currently being evaluated includes potential treatment for various diarrheic syndromes, motility disorders (post-operative ileus, constipation), and visceral pain (post operative pain, irritable bowel syndrome, and inflammatory bowel disorders) (Pierre J. M. Riviere and Jean-Louis Junien, "Opioid receptors: Targets for new gastrointestinal drug development" Drug Development, 2000, pp. 203-238).

Around the same time the opioid receptors were identified, the enkephalins were identified as a set of endogenous opioid ligands (D. S. Fries, "Analgesics", in *Principles of Medicinal Chemistry,* 4th ed.; W. O. Foye; T. L. Lemke, and D. A. Williams, Eds.; Williams and Wilkins: Baltimore, Md., 1995; pp. 247-269). Schiller discovered that truncating the original pentapeptide enkephalins to simplified dipeptides yielded a series of compounds that maintained opioid activity (Schiller, P. WO 96/06855). However one potential drawback cited for such compounds is the likelihood of their inherent instability (P. W. Schiller et al., Int. J. Pept. Protein Res. 1993, 41 (3), pp. 313-316).

More recently, a series of opioid pseudopeptides containing heteroaromatic or heteroaliphatic nuclei were disclosed, however this series is reported showing a different functional profile than that described in the Schiller works. (L. H. Lazarus et al., *Peptides* 2000, 21, pp. 1663-1671)

Most recently, works around morphine related structures were reported by Wentland, et al, where carboxamido morphine derivatives and it's analogs were prepared (M. P. Wentland et al., *Biorg. Med. Chem. Letters* 2001, 11, pp. 1717-1721; M. P. Wentland et al., *Biorg. Med. Chem. Letters* 2001, 11, pp. 623-626). Wentland found that substitution for the phenol moiety of the morphine related structures with a primary carboxamide led anywhere from equal activities up to 40 fold reduced activities, depending on the opioid receptor and the carboxamide. It was also revealed that any additional N-substitutions on the carboxamide significantly diminished the desired binding activity.

Compounds of the present invention have not been previously disclosed and are believed to provide advantages over related compounds by providing improved pharmacological profiles.

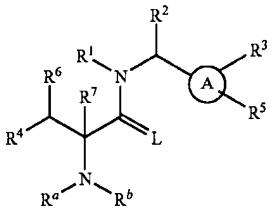
Opioid receptor modulators, agonists or antagonists are useful in the treatment and prevention of various mammalian disease states, for example pain and gastrointestinal disorders such as diarrheic syndromes, motility disorders including post-operative ileus and constipation, and visceral pain including post-operative pain, irritable bowel syndrome and inflammatory bowel disorders.

It is an object of the present invention to provide opioid receptor modulators. It is a further object of the invention to provide opioid receptor agonists and opioid receptor antagonists. It is an object of the present invention to provide opioid receptor ligands that are selective for each type of opioid receptor, mu, delta and kappa. It is a further object of the present invention to provide opioid receptor ligands that modulate two or three opioid receptor types, mu, delta and kappa, simultaneously. It is an object of the invention to provide certain instant compounds that are also useful as intermediates in preparing new opioid receptor modulators. It is also an object of the invention to provide a method of treating or ameliorating a condition mediated by an opioid receptor. And, it is an object of the invention to provide a useful pharmaceutical composition comprising a compound of the present invention useful as an opioid receptor modulator.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula (I)

Formula (I)



wherein:

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocyclyl, aryl(C_{1-6})alkyl, and heteroaryl(C_{1-6})alkyl; wherein aryl of aryl(C_{1-6})alkyl is optionally fused to a heterocyclyl or cycloalkyl;

and wherein the cycloalkyl and heterocyclyl of R^1 are optionally substituted with C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, hydroxy, cyano, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, halogen, carboxy, aryl(C_{1-6})alkoxycarbonyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, or aminosulfonyl;

and, wherein C_{1-6}alkyl of R^1 is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkoxy, aryl, cycloalkyl, heterocyclyl, hydroxy, cyano, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, halogen, and carboxy;

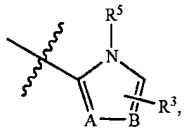
and wherein the aryl and heteroaryl portion of aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-6}alkyl; hydroxy(C_{1-6})alkyl; C_{1-6}alkoxy; aryl(C_{1-6})alkyl; aryl(C_{1-6})alkoxy; aryl; heteroaryl optionally substituted with C_{1-4}alkyl; cycloalkyl; heterocyclyl; aryloxy; heteroaryloxy; cycloalkyloxy; heterocyclyloxy; amino; C_{1-6}alkylamino; (C_{1-6}alkyl)$_2$amino; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-6})alkylaminocarbonyl; arylaminocarbonyl wherein aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; heterocyclylcarbonyl; carboxy; C_{1-6}alkoxycarbonyl; C_{1-6}alkylcarbonyl; C_{1-6}alkylcarbonylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl; (C_{1-6}alkyl)$_2$aminocarbonyl; cyano; halogen; trifluoromethyl; trifluoromethoxy; or hydroxy;

R^2 is selected from the group consisting of hydrogen, C_{1-8}alkyl, hydroxy(C_{1-8})alkyl, aryl(C_{1-6})alkoxy(C_{1-6})alkyl, or aryl(C_{1-8})alkyl;

wherein the aryl portion of the aryl-containing substituents of R^2 are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, cyano, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy; and wherein alkyl and alkoxy substituents of aryl are optionally substituted with hydroxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, or aryl;

A is selected from the group consisting of aryl, ring system a-1, a-2, a-3, and a-4, optionally substituted with R^3 and R^5;

a-1



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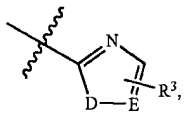
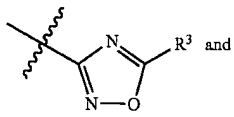
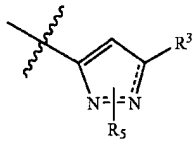


a-3



and

a-4



wherein

A-B is selected from the group consisting of N-C, C-N, N-N and C-C;

D-E is selected from the group consisting of O-C, S-C, and O-N;

R^3 is one to two substituents independently selected from the group consisting of C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl, heteroaryl(C_{2-6})alkynyl, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, arylamino, heteroarylamino, aryloxy, heteroaryloxy, and halogen;

wherein the aryl and heteroaryl portion of R^3 are optionally substituted with one to five substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, aryl(C_{1-6})alkyl, aryl(C_{1-6})alkoxy, aryl, aryloxy, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkoxy, heteroaryl, heteroaryloxy, arylamino, heteroarylamino, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, carboxy(C_{1-6})alkylamino, carboxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbonylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, carboxy(C_{1-6})alkylaminocarbonyl, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxy, C_{1-6}alkylsulfonyl, C_{1-6}alkylsulfonylamino, —C(O)—NH—CH(—R^c)—C(O)—NH_2, and C_{1-6}alkyl;

wherein C_{1-6}alkyl of R^3 is optionally substituted with a substituent selected from the group consisting of hydroxy, carboxy, C_{1-4}alkoxycarbonyl, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, aminocarbonyl, (C_{1-4})alkylaminocarbonyl, di(C_{1-4})alkylaminocarbonyl, aryl, heteroaryl, arylamino, heteroarylamino, aryloxy, heteroaryloxy, aryl(C_{1-4})alkoxy, and heteroaryl(C_{1-4})alkoxy;

R^c is selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbonylamino, aryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkyl, aryl, and heteroaryl;

R^4 is aryl or heteroaryl; wherein R^4 is optionally substituted with one to five substituents independently selected from the group R^{41}; wherein R^{41} is (C_{1-6})alkyl, (C_{1-6})alkoxy, aryl(C_{1-6})alkoxy, aryl(C_{1-6})alkylcarbonyloxy, heteroaryl(C_{1-6})alkylcarbonyloxy, heteroaryl, hydroxy, halogen,

aminosulfonyl, formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, $(C_{1-6}alkyl)_2$aminocarbonyl, heterocyclylcarbonyl, carboxy, or cyano; and wherein C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or $(C_{1-6}alkyl)_2$amino; and wherein the aryl portion of aryl (C_{1-6})alkylcarbonyloxy is optionally substituted with one to four substituents independently selected from the group consisting of (C_{1-6})alkyl, (C_{1-6})alkoxy, halogen, cyano, amino, and hydroxy;

R^5 is a substituent on a nitrogen atom contained in ring A selected from the group consisting of hydrogen, C_{1-4}alkyl, and aryl;

R^6 is selected from the group consisting of hydrogen and C_{1-6}alkyl;

R^7 is selected from the group consisting of hydrogen and C_{1-6}alkyl;

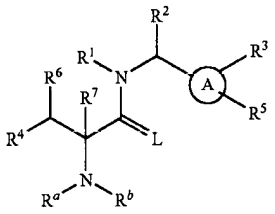
R^a and R^b are substituents independently selected from the group consisting of hydrogen and C_{1-6}alkyl; or, when R^a and R^b are other than hydrogen, R^a and R^b are optionally taken together with the nitrogen to which they are both attached to form a five to eight membered monocyclic ring;

L is selected from the group consisting of O, S, and $N(R^d)$; wherein R^d is hydrogen, C_{1-6}alkyl, or aryl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

The present invention is also directed to compounds of Formula (I)

Formula (I)



wherein:

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocyclyl, aryl(C_{1-6})alkyl, and heteroaryl(C_{1-6})alkyl; wherein when R^1 is phenyl(C_{1-6})alkyl, phenyl is optionally fused to a heterocyclyl or cycloalkyl;

wherein when R^1 is C_{1-2}alkyl, said C_{1-2}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkoxy, aryl, cycloalkyl, heterocyclyl, hydroxy, cyano, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, trifluoromethyl, and carboxy;

and further, wherein when R^1 is C_{3-6}alkyl, said C_{3-6}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkoxy, aryl, cycloalkyl, heterocyclyl, hydroxy, cyano, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, trifluoromethyl, and carboxy;

wherein the cycloalkyl and heterocyclyl of C_{1-2}alkyl and C_{3-6}alkyl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, hydroxy, cyano, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, trifluoromethyl, carboxy, aryl(C_{1-6})alkoxycarbonyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, $(C_{1-6}alkyl)_2$aminocarbonyl, and aminosulfonyl;

furthermore, wherein the cycloalkyl and heterocyclyl of R^1 are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, hydroxy, cyano, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, trifluoromethyl, carboxy, aryl(C_{1-6})alkoxycarbonyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, $(C_{1-6}alkyl)_2$aminocarbonyl, and aminosulfonyl;

furthermore, wherein the aryl and heteroaryl portion of the R^1 substituents aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl, are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-6}alkyl; hydroxy(C_{1-6})alkyl; C_{1-6}alkoxy; C_{6-10}aryl(C_{1-6})alkyl; C_{6-10}aryl(C_{1-6})alkoxy; C_{6-10}aryl; heteroaryl optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, and carboxy; cycloalkyl; heterocyclyl; C_{6-10}aryloxy; heteroaryloxy; cycloalkyloxy; heterocyclyloxy; amino; C_{1-6}alkylamino; $(C_{1-6}alkyl)_2$amino; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-6})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; heterocyclylcarbonyl; carboxy; C_{1-6}alkylcarbonyloxy; C_{1-6}alkoxycarbonyl; C_{1-6}alkylcarbonyl; C_{1-6}alkylcarbonylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl; $(C_{1-6}alkyl)_2$aminocarbonyl; cyano; halogen; trifluoromethyl; trifluoromethoxy; and hydroxy;

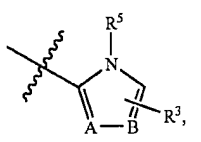
provided that no more than one R^{11} substituent is selected from the group consisting of C_{6-10}aryl(C_{1-6})alkyl; C_{6-10}aryl(C_{1-6})alkoxy; C_{6-10}aryl; heteroaryl optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, and carboxy; cycloalkyl; heterocyclyl; C_{6-10}aryloxy; heteroaryloxy; cycloalkyloxy; C_{6-10}arylaminocarbonyl, heterocyclylcarbonyl; and heterocyclyloxy;

R^2 is hydrogen, C_{1-8}alkyl, hydroxy(C_{1-8})alkyl, C_{6-10}aryl(C_{1-6})alkoxy(C_{1-6})alkyl, or C_{6-10}aryl(C_{1-8})alkyl;

wherein the C_{6-10}aryl group in the C_{6-10}aryl-containing substituents of R^2 are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, $(C_{1-6}alkyl)_2$aminocarbonyl, cyano, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy; and, wherein the C_{1-6}alkyl and C_{1-6}alkoxy substituents of aryl are optionally substituted with hydroxy, amino, C_{1-6}alkylamino, $(C_{1-6}alkyl)_2$amino, or C_{1-6} aryl;

A is selected from the group consisting of aryl, ring system a-1, a-2, a-3, and a-4, optionally substituted with R^3 and R^5;

a-1



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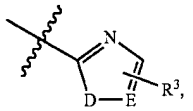

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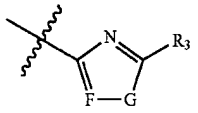

and

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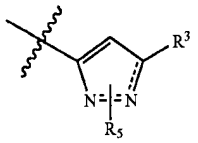


wherein

A-B is selected from the group consisting of N-C, C-N, N-N and C-C;

D-E is selected from the group consisting of O-C, S-C, and O-N;

F-G is selected from the group consisting of N-O and C-O;

R^3 is one to two substituents independently selected from the group consisting of C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl, heteroaryl(C_{2-6})alkynyl, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, arylamino, heteroarylamino, aryloxy, heteroaryloxy, trifluoromethyl, and halogen;

wherein the aryl, heteroaryl and the aryl and heteroaryl of aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{2-6})alkenyl, heteroaryl(C_{2-6})alkynyl, arylamino, heteroarylamino, aryloxy, and heteroaryloxy, are optionally substituted with one to five fluoro substituents or one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, C_{6-10}aryl(C_{1-6})alkyl, C_{6-10}aryl(C_{1-6})alkoxy, C_{6-10}aryl, C_{6-10}aryloxy, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkoxy, heteroaryl, heteroaryloxy, C_{6-10}arylamino, heteroarylamino, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, carboxy(C_{1-6})alkylamino, carboxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbonylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, carboxy(C_{1-6})alkylaminocarbonyl, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxy, C_{1-6}alkylsulfonyl, and C_{1-6}alkylsulfonylamino; provided that no more than one such substituent on the aryl or heteroaryl portion of R^3 is selected from the group consisting of C_{6-10}aryl(C_{1-6})alkyl, C_{6-10}aryl(C_{1-6})alkoxy, C_{6-10}aryl, C_{6-10}aryloxy, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkoxy, heteroaryl, heteroaryloxy, C_{6-10}arylamino, and heteroarylamino;

and wherein C_{1-6}alkyl, and C_{1-6}alkyl of aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl is optionally substituted with a substituent selected from the group consisting of hydroxy, carboxy, C_{1-4}alkoxycarbonyl, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, aminocarbonyl, (C_{1-4})alkylaminocarbonyl, di(C_{1-4})alkylaminocarbonyl, aryl, heteroaryl, arylamino, heteroarylamino, aryloxy, heteroaryloxy, aryl(C_{1-4})alkoxy, and heteroaryl(C_{1-4})alkoxy;

R^4 is C_{6-10}aryl or a heteroaryl selected from the group consisting of furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, quinolizinyl, quinolinyl, isoquinolinyl and quinazolinyl;

wherein R^4 is optionally substituted with one to three R^{41} substituents independently selected from the group consisting of (C_{1-6})alkyl optionally substituted with amino, C_{1-6}alkylamino, or (C_{1-6}alkyl)$_2$amino; (C_{1-6})alkoxy; phenyl(C_{1-6})alkoxy; phenyl(C_{1-6})alkylcarbonyloxy wherein the C_{1-6} alkyl is optionally substituted with amino; a non fused 5-membered-heteroaryl(C_{1-6})alkylcarbonyloxy; a non fused 5-membered-heteroaryl; hydroxy; halogen; aminosulfonyl; formylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl wherein C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or (C_{1-6}alkyl)$_2$amino; (C_{1-6}alkyl)$_2$aminocarbonyl wherein each C_{1-6}alkyl is optionally substituted with amino, C_{1-6}alkylamino, or (C_{1-6}alkyl)$_2$amino; heterocyclylcarbonyl wherein heterocyclyl is a 5-7 membered nitrogen-containing ring and said heterocyclyl is attached to the carbonyl carbon via a nitrogen atom; carboxy; or cyano; and wherein the phenyl portion of phenyl(C_{1-6})alkylcarbonyloxy is optionally substituted with (C_{1-6})alkyl (C_{1-6})alkoxy, halogen, cyano, amino, or hydroxy;

provided that no more than one R^{41} is (C_{1-6})alkyl substituted with C_{1-6}alkylamino or (C_{1-6}alkyl)$_2$amino; aminosulfonyl; formylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl; (C_{1-6}alkyl)$_2$aminocarbonyl; heterocyclylcarbonyl; hydroxy; carboxy; or a phenyl- or heteroaryl-containing substituent;

R^5 is a substituent on a nitrogen atom of ring A selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^6 is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen or C_{1-6}alkyl;

R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and C_{1-6}alkoxycarbonyl; alternatively, when R^a and R^b are each other than hydrogen, R^a and R^b are optionally taken together with the nitrogen atom to which they are both attached to form a five to eight membered monocyclic ring;

L is selected from the group consisting of O, S, and N(R^d) wherein R^d is hydrogen or C_{1-6}alkyl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

Illustrative of the invention is a pharmaceutically acceptable carrier and any of the compounds described above.

The present invention is also directed to methods for producing the instant compounds of Formula (I) and pharmaceutical compositions and medicaments thereof.

The present invention is further directed to methods for treating opioid modulated disorders such as pain and gastrointestinal disorders. Compounds of the present invention are believed to provide advantages over related compounds by providing improved pharmacological profiles. Further specific embodiments of preferred compounds are provided hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows a schematic of the protocol to determine visceral hyperalgesia in rats.

FIG. **2** and FIG. **3** each show the effect in rat of Cpd 18 on the hyperalgesic response to colorectal balloon distention following zymosan.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention include those compounds wherein R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, aryl(C_{1-4})alkyl, and heteroaryl(C_{1-4})alkyl;

wherein the aryl and heteroaryl portion of aryl(C_{1-4})alkyl and heteroaryl(C_{1-4})alkyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-6}alkoxy; heteroaryl optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, and carboxy; carboxy; C_{1-4}alkoxycarbonyl; C_{1-4}alkoxycarbonyloxy; aminocarbonyl; C_{1-4}alkylaminocarbonyl; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-6})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; heterocyclylcarbonyl; cyano; halogen; trifluoromethoxy; or hydroxy; provided that no more than one R^{11} is heteroaryl (optionally substituted with one to two C_{1-4}alkyl substituents); C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; or heterocyclylcarbonyl.

Embodiments of the present invention include those compounds wherein R^1 is selected from the group consisting of C_{6-10}aryl(C_{1-4})alkyl, pyridinyl(C_{1-4})alkyl, and furanyl(C_{1-4})alkyl; wherein C_{6-10}aryl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-3}alkoxy; tetrazolyl; carboxy; C_{1-4}alkoxycarbonyl; aminocarbonyl; C_{1-4}alkylaminocarbonyl; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; cyano; halogen; and trifluoromethoxy; provided that that no more than one R^{11} is C_{6-10}arylaminocarbonyl.

Embodiments of the present invention include those compounds wherein R^1 is selected from the group consisting of phenyl(C_{1-3})alkyl, pyridinyl(C_{1-3})alkyl, and furanyl(C_{1-3})alkyl; wherein phenyl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-3}alkoxy; tetrazolyl, C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; chloro; fluoro; trifluoromethoxy; C_{1-4}alkoxycarbonyl; and carboxy; provided that that no more than one R^{11} is C_{6-10}arylaminocarbonyl.

Embodiments of the present invention include those compounds wherein R^1 is phenylmethyl, pyridinylmethyl, or furanylmethyl; wherein phenyl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of methoxy; tetrazolyl; cyclopropylaminocarbonyl; (2-hydroxyeth-1-yl) aminocarbonyl; methoxycarbonyl; phenylaminocarbonyl wherein phenyl is optionally substituted with carboxy; morpholin-4-ylcarbonyl; and carboxy; provided that that no more than one R^{11} is phenylaminocarbonyl.

Embodiments of the present invention include those compounds wherein R^2 is a substituent selected from the group consisting of hydrogen, C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, and phenyl(C_{1-6})alkoxy(C_{1-4})alkyl;

wherein said phenyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkoxy, hydroxy, cyano, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy.

Embodiments of the present invention include those compounds wherein R^2 is selected from the group consisting of hydrogen and C_{1-4}alkyl.

Embodiments of the present invention include those compounds wherein R^2 is hydrogen or methyl.

Embodiments of the present invention include those compounds wherein ring A is a-1.

Embodiments of the present invention include those compounds wherein A-B of ring a-1 is selected from the group consisting of N—C and O—N.

Embodiments of the present invention include those compounds wherein A-B of ring a-1 is N—C.

Embodiments of the present invention include those compounds wherein R^3 is one to two substituents independently selected from the group consisting of C_{1-6}alkyl, halogen, and aryl; wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, carboxy, aminocarbonyl, C_{1-3}alkylsulfonylamino, cyano, hydroxy, amino, C_{1-3}alkylamino, and $(C_{1-3}alkyl)_2$amino.

Embodiments of the present invention include those compounds wherein R^3 is one to two substituents independently selected from the group consisting of C_{1-3}alkyl, bromo, and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro, fluoro, iodo, carboxy, aminocarbonyl, and cyano.

Embodiments of the present invention include those compounds wherein R^3 is one to two substituents independently selected from the group consisting of methyl and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro and carboxy.

Embodiments of the present invention include those compounds wherein at least one R^3 substituent is phenyl.

Embodiments of the present invention include those compounds wherein R^3 is a substituent selected from the group consisting of methyl and phenyl optionally substituted with one to two substituents independently selected from the group consisting of chloro and carboxy.

Embodiments of the present invention include those compounds wherein R^4 is C_{6-10}aryl optionally substituted with one to three R^{41} substituents independently selected from the group consisting of (C_{1-3})alkyl, (C_{1-6})alkoxy, phenyl(C_{1-6})alkoxy; hydroxy; halogen; formylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl; $(C_{1-6}alkyl)_2$aminocarbonyl; heterocyclylcarbonyl wherein heterocyclyl is a 5-7 membered nitrogen-containing ring and said heterocyclyl is attached to the carbonyl carbon via a nitrogen atom; carboxy; and cyano; provided that no more than one R^{41} substituent is formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, $(C_{1-6}alkyl)_2$aminocarbonyl, heterocyclylcarbonyl, hydroxy, carboxy, or a phenyl-containing substituent.

Embodiments of the present invention include those compounds wherein R^4 is phenyl substituted with one to three R^{41} substituents independently selected from the group consisting of (C_{1-3})alkyl, (C_{1-3})alkoxy, phenyl(C_{1-3})alkoxy, hydroxy, C_{1-6}alkylaminocarbonyl, and aminocarbonyl; provided that no more than one R^{41} substitutent is aminocarbonyl, C_{1-6}alkylaminocarbonyl, hydroxy, or a phenyl-containing substituent.

Embodiments of the present invention include those compounds wherein R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two substituents independently selected from the group consisting of methyl, methoxy, and benzyloxy.

Embodiments of the present invention include those compounds wherein R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two methyl substituents.

Embodiments of the present invention include those compounds wherein R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and substituted at the 2- and 6-positions with methyl substituents.

Embodiments of the present invention include those compounds wherein R^5 is hydrogen or methyl.

Embodiments of the present invention include those compounds wherein R^5 is hydrogen.

Embodiments of the present invention include those compounds wherein R^6 is hydrogen or methyl.

Embodiments of the present invention include those compounds wherein R^6 is hydrogen.

Embodiments of the present invention include those compounds wherein R^7 is hydrogen or methyl.

Embodiments of the present invention include those compounds wherein R^7 is hydrogen.

Embodiments of the present invention include those compounds wherein R^a and R^b are independently selected from the group consisting of hydrogen and C_{1-3}alkyl; or, when R^a and R^b are each other than hydrogen or C_{1-6} alkoxycarbonyl, R^a and R^b are optionally taken together with the nitrogen atom to which they are both attached to form a five to seven membered monocyclic ring.

Embodiments of the present invention include those compounds wherein R^a and R^b are independently hydrogen or methyl.

Embodiments of the present invention include those compounds wherein R^a and R^b are each hydrogen.

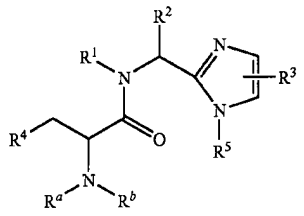
Embodiments of the present invention include those compounds wherein L is O.

Embodiments of the present invention include those compounds that are present in their RR, SS, RS, or SR configuration.

Embodiments of the present invention include those compounds that are present in their S,S configuration.

An aspect of the present invention includes compounds of Formula (Ia):

Formula (Ia)



wherein:

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, aryl(C_{1-4})alkyl, and heteroaryl(C_{1-4})alkyl;

wherein the aryl and heteroaryl portion of aryl(C_{1-4})alkyl and heteroaryl(C_{1-4})alkyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-6}alkoxy; heteroaryl optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, and carboxy; carboxy; C_{1-4}alkoxycarbonyloxy; C_{1-4}alkoxycarbonyl; aminocarbonyl; C_{1-4}alkylaminocarbonyl; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-6})alkylaminocarbonyl; C_{6-10}-arylaminocarbonyl wherein C_{6-10}-aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; heterocyclylcarbonyl; cyano; halogen; trifluoromethoxy; and hydroxy; provided that no more than one R^{11} is heteroaryl (optionally substituted with one to two C_{1-4}alkyl substituents); C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; or heterocyclylcarbonyl;

R^2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, and phenyl(C_{1-6})alkoxy (C_{1-4})alkyl;

wherein said phenyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkoxy, hydroxy, cyano, fluorine, chlorine, bromine, trifluoromethyl, and trifluoromethoxy;

R^3 is one to two substituents independently selected from the group consisting of C_{1-6}alkyl, halogen, and aryl; wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, carboxy, aminocarbonyl, C_{1-3}alkylsulfonylamino, cyano, hydroxy, amino, C_{1-3}alkylamino, and (C_{1-3}alkyl)$_2$amino;

R^4 is C_{6-10}aryl optionally substituted with one to three R^{41} substituents independently selected from the group consisting of (C_{1-3})alkyl, (C_{1-6})alkoxy, phenyl(C_{1-6})alkoxy; hydroxy; halogen; formylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl; (C_{1-6}alkyl)$_2$aminocarbonyl; heterocyclylcarbonyl wherein heterocyclyl is a 5-7 membered nitrogen-containing ring and said heterocyclyl is attached to the carbonyl carbon via a nitrogen atom; carboxy; and cyano;

provided that no more than one R^{41} substituent is formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, heterocyclylcarbonyl, hydroxy, carboxy, or a phenyl-containing substituent.

R^5 is hydrogen or methyl;

R^a and R^b are independently hydrogen or C_{1-3}alkyl; or, when R^a and R^b are each other than hydrogen, R^a and R^b are optionally taken together with the nitrogen atom to which they are both attached to form a five to seven membered monocyclic ring;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

Another aspect of the present invention is directed to a compound of Formula (Ia) wherein:

R^1 is selected from the group consisting of C_{6-10}aryl(C_{1-4})alkyl, pyridinyl(C_{1-4})alkyl, and furanyl(C_{1-4})alkyl; wherein C_{6-10}aryl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-3}alkoxy; tetrazolyl; carboxy; C_{1-3}alkoxycarbonyl; aminocarbonyl; C_{1-4}alkylaminocarbonyl; C_{1-3}alkylaminocarbonyl; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; cyano; halogen; and trifluoromethoxy; provided that no more than one R^{11} is C_{6-10}arylaminocarbonyl;

R^2 is hydrogen or C_{1-4}alkyl;

R^3 is one to two substituents independently selected from the group consisting of C_{1-3}alkyl, bromo, and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro, fluoro, carboxy, aminocarbonyl, and cyano;

R^4 is phenyl substituted with one to three R^{41} substituents independently selected from the group consisting of (C_{1-3})alkyl, (C_{1-3})alkoxy, phenyl(C_{1-3})alkoxy, hydroxy, C_{1-6}alkylaminocarbonyl, and aminocarbonyl; provided

that no more than one R^{41} is aminocarbonyl, C_{1-6}alkylaminocarbonyl, hydroxy, or a phenyl-containing substituent;

R^5 is hydrogen;

R^a and R^b are independently hydrogen or methyl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

Another aspect of the present invention is directed to a compound of Formula (Ia) wherein:

R^1 is selected from the group consisting of phenyl(C_{1-3})alkyl, pyridinyl(C_{1-3})alkyl, and furanyl(C_{1-3})alkyl; wherein phenyl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-3}alkoxy; tetrazolyl, C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; chloro; fluoro; trifluoromethoxy; and carboxy;

R^2 is hydrogen or methyl;

R^3 is one to two substituents independently selected from the group consisting of methyl and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro and carboxy;

R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two substituents independently selected from the group consisting of methyl, methoxy, and benzyloxy;

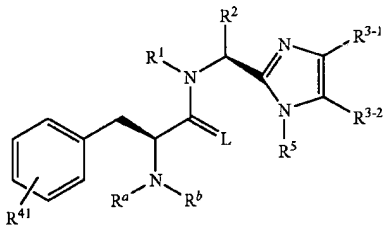
R^5 is hydrogen;

R^a and R^b are each hydrogen;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

Another embodiment is directed to compounds of Formula (Ib):

Formula (Ib)



wherein in one embodiment of this invention the variables are as previously defined. In another embodiment of the present invention L is oxygen and R^1, R^2, R^{3-1}, R^{3-2}, R^5, R^a, R^b, and R^{41} are dependently selected from the group consisting of:

TABLE I

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
1	2-Aminocarbonyl-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
2	2-Cyano-phenyl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
3	2-Bromo-phenyl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
4	3-Carboxy-4-methoxy-phenyl methyl	methyl	phenyl	H	H	4-aminocarbonyl	H
5	3-Carboxy-4-methoxy-phenyl methyl	H	phenyl	H	H	4-aminocarbonyl	H
6	3-Carboxy-4-methoxy-phenyl methyl	H	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
7	3-Methoxycarbonyl-4-methoxy-phenylmethyl	H	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
8	3-(1H-tetrazol-5-yl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
9	3-Methoxycarbonyl-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
10	3-Methoxy carbonyl-phenylmethyl	methyl	naphthalen-1-yl	H	H	2,6-dimethyl-4-aminocarbonyl	H
11	3-Carboxy-phenylmethyl	methyl	naphthalen-1-yl	H	H	2,6-dimethyl-4-aminocarbonyl	H
12	3-Carboxy-phenylmethyl	methyl	4-chlorophenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
13	4-Carboxy-phenylmethyl	methyl	naphthalen-1-yl	H	H	2,6-dimethyl-4-aminocarbonyl	H
14	3-Methoxy-4-carboxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
15	3,4-Dihydroxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
16	Piperidin-4-yl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
17	3-Methoxy carbonyl-4-methoxy--phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H

TABLE I-continued

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
18	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
19	3,4-Dimethoxy-phenylmethyl	methyl	3-bromophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
20	3,4-Dimethoxy-phenylmethyl	methyl	3-carboxyphenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
21	3,4-Dimethoxy-phenylmethyl	benzyloxy-methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
23	3,4-Dimethoxy-phenylmethyl	methyl	3-aminocarbonyl phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
24	3,4-Dimethoxy-phenylmethyl	methyl	3-cyanophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
25	Isopropyl	H	quinoxalin-8-yl	Me	H	2,6-dimethyl-4-hydroxy	H
26	3,4-Dimethoxy-phenylmethyl	methyl	2-bromophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
27	3,4-Dimethoxy-phenylmethyl	methyl	2-cyanophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
28	3,4-Dimethoxy-phenylmethyl	methyl	2-aminocarbonyl phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
29	3,4-Dimethoxy-phenylmethyl	methyl	2-carboxyphenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
30	3,4-Dibenzyloxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
31	[1,3]benzo dioxal-5-yl	methyl	phenyl	H	H	2,6-dimethyl, 4-hydroxy	H
32	4-Methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
33	3-Methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
34	2,4-Dimethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
35	3,4-Dimethoxy-phenylmethyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
36	Isopropyl	H	4-methylcarbonyl phenyl	H	H	2,6-dimethyl-4-hydroxy	H
37	Isopropyl	H	3-fluoro, 4-carboxy-phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
38	Isopropyl	H	2-phenyl-ethylen-1-yl	Me	H	2,6-dimethyl-4-hydroxy	H
39	Isopropyl	H	4-hydroxymethyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
40	Benzhydryl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
41	Isopropyl	H	4-cyanophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
42	Benzyl	methyl	4-trifluoromethyl phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
43	Isopropyl	H	3-trifluoromethoxy phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
44	Isopropyl	H	4-trifluoromethoxy phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
45	Isopropyl	H	3-methanesulfonyl aminophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
46	Isopropyl	H	4-(2-carboxyethyl) phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
47	Isopropyl	H	3-amino-5-carboxyphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
48	3-Carboxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
49	4-Carboxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-carboxy	H
50	4-Carboxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
51	4-Methoxy carbonyl-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
52	3-Methoxy carbonyl-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H

TABLE I-continued

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
53	1-Benzyloxy carbonyl-piperadin-4-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
54	Furan-2-yl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
55	Furan-3-yl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
56	Cyclohexyl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
57	Pyridin-4-yl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
58	Benzyl	methyl	4-chlorophenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
59	Benzyl	methyl	3-fluorophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
60	Isopropyl	H	3-cyanophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
61	Isopropyl	H	2,5-difluorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
62	Isopropyl	H	4-methanesulfonyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
64	Benzyl	benzyloxy methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
65	Isopropyl	H	Br	Me	H	2,6-dimethyl-4-hydroxy	H
66	Isopropyl	H	4-dimethylamino phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
67	Isopropyl	H	3-dimethylamino carbonylphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
68	Isopropyl	H	3-hydroxyphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
69	Isopropyl	H	4-aminocarbonyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
70	Isopropyl	H	3-chlorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
71	Isopropyl	H	2,4-difluorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
72	Isopropyl	H	3-methanesulfonyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
73	Isopropyl	H	3-aminocarbonyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
74	Benzyl	methyl	4-trifluoromethyl phenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
75	3,4-Dimethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
76	Benzyl	methyl	4-fluorophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
77	4-Dimethylamino-phenylmethyl	methyl	phenyl	H	Me	2,6-dimethyl-4-hydroxy	H
78	4-Methylamino-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
79	4-Methylcarbonyl amino-phenyl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
80	4-Carboxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
81	4 Hydroxy phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
83	Benzyl	methyl	4-fluorophenyl	H	H	2,6-dimethyl-4-hydroxy	H
84	Isopropyl	methyl	4-fluorophenyl	H	H	2,6-dimethyl-4-hydroxy	H
85	Isopropyl	hydroxy methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
86	Isopropyl	H	phenyl	H	H	2,6-dimethyl, 4-aminocarbonyl	H
87	3,4-Dichloro-phenylmethyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
88	4-Methylcarbonyl oxy-phenyl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
89	4-Methoxy carbonyl-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H

TABLE I-continued

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
90	3-Aminocarbonyl-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
91	3-Cyano-phenyl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
92	Pyridin-3-yl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
93	Pyridin-2-yl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
94	1-(R)-Phenylethyl	H	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
95	1-(S)-Phenylethyl	H	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
96	2-Methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
97	2,6-Dichloro-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
98	3-Phenoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
99	Naphthalen-1-yl-methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
100	Naphthalen-2-yl-methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
101	3-Bromo-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
102	3,4-Dimethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
103	2,4-Dichloro-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
104	Benzyl	isobutyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
105	Benzyl	benzyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
106	Benzyl	isopropyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
107	Benzyl	H	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
108	3-Phenyl prop-1-yl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
109	2-Phenylethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
111	1-Phenylethyl diastereomer A	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
112	1-Phenylethyl diasteromer B	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
114	Benzyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
115	Isopropyl	H	4-biphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
116	Isopropyl	H	3-fluorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
117	Isopropyl	H	2-fluorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
118	Isopropyl	hydroxy methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
119	H	hydroxy methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
120	Isopropyl	3-(amino methyl) phenylmethyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
121	Isopropyl	3-(amino carbonyl phenylmethyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
122	Isopropyl	3-cyano phenylmethyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
123	Isopropyl	H	4-carboxyphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
124	Isopropyl	H	pyridin-3-yl	Me	H	2,6-dimethyl-4-hydroxy	H
125	Isopropyl	H	4-methoxyphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
126	Isopropyl	H	3,5-difluorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
127	Cyclohexyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
129	Carboxymethyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H

TABLE I-continued

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
130	Isopropyl	H	3-hydroxymethyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
131	Isopropyl	H	pyrimidin-5-yl	Me	H	2,6-dimethyl-4-hydroxy	H
132	Isopropyl	H	pyrimidin-5-yl	Me	H	4-hydroxy	H
133	Isopropyl	H	3-carboxyphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
134	Isopropyl	H	3-biphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
135	Isopropyl	H	2-methoxyphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
136	Isopropyl	benzyl	phenyl	H	H	3-aminocarbonyl	H
137	Isopropyl	isopropyl	phenyl	H	H	3-aminocarbonyl	H
138	Isopropyl	benzyloxy methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
139	Isopropyl	isobutyl	phenyl	H	H	2,6-dimethyl-4-[2-(2,6-dimethyl-4-hydroxyphenyl)-1-amino-ethylcarbonxyloxy]phenyl	H
140	Isopropyl	isobutyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
141	Isopropyl	H	3,5-dichlorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
142	Isopropyl	H	3-methoxyphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
143	Isopropyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
145	Isopropyl	H	2-biphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
146	Isopropyl	H	thiophen-3-yl	Me	H	2,6-dimethyl-4-hydroxy	H
147	Isopropyl	H	4-chlorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
148	Isopropyl	H	3-methylcarbonyl aminophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
149	Isopropyl	H	4-trifluoromethyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
150	Isopropyl	H	naphthalen-2-yl	Me	H	2,6-dimethyl-4-hydroxy	H
151	Isopropyl	H	2-trifluoromethyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
152	Isopropyl	H	thiophen-3-yl	Me	H	4-hydroxy	H
153	Isopropyl	H	pyridin-3-yl	Me	H	4-hydroxy	H
154	Isopropyl	H	phenyl	Me	H	4-hydroxy	H
155	Isopropyl	H	2-chlorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
156	Isopropyl	H	naphthalen-1-yl	Me	H	2,6-dimethyl-4-hydroxy	H
157	Isopropyl	benzyl	phenyl	H	H	3-cyano	H
158	Isopropyl	benzyl	phenyl	H	H	4-hydroxy	H
159	Isopropyl	benzyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
160	Isopropyl	isopropyl	phenyl	H	H	3-cyano	H
161	Isopropyl	isopropyl	phenyl	H	H	4-hydroxy	H
162	Isopropyl	isopropyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
163	Isopropyl	H	4-fluorophenyl	Me	H	2,6-dimethyl-4-hydroxy	H
164	Isopropyl	H	3,5-bis-trifluoromethyl phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
165	Isopropyl	H	2-methylphenyl	Me	H	2,6-dimethyl-4-hydroxy	H
166	Isopropyl	H	phenyl	Me	H	2,6-dimethyl-4-hydroxy	H
167	2-Dimethylamino-1-methyl-eth-1-yl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
168	Methyl	isobutyl	phenyl	H	H	3-aminocarbonyl	H
169	Methyl	isobutyl	phenyl	H	H	3-cyano	H
170	Ethyl	isopropyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
171	Methyl	isopropyl	phenyl	H	H	4-hydroxy	H
172	H	3-amino carbonyl phenyl methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H

TABLE I-continued

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
173	H	3-cyano phenyl methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
174	Methyl	isobutyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
175	H	benzyloxy methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
176	H	isobutyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
177	H	benzyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
178	Isopropyl	H	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
179	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-morpholin-1-ylcarbonyl	H
181	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-ethyl aminocarbonyl	H
183	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-methyl aminocarbonyl	H
185	H	isopropyl	phenyl	H	H	3-aminocarbonyl	H
186	H	isopropyl	phenyl	H	H	3-cyano	H
187	H	isopropyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
188	H	isopropyl	phenyl	H	H	4-hydroxy	H
189	Methyl	methyl	phenyl	H	H	4-aminosulfonyl	H
190	Cyclohexyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
191	Cyclohexyl	H	phenyl	H	H	4-hydroxy	H
192	Cyclopropyl methyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
193	Cyclopropyl methyl	H	phenyl	H	H	4-hydroxy	H
194	Isopropyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
195	Isopropyl	H	phenyl	H	H	4-hydroxy	H
196	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
197	Ethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
198	Methyl	H	phenyl	H	H	4-hydroxy	H
199	Methyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
202	Methyl	methyl	phenyl	H	H	4-aminocarbonyl	H
204	Methyl	methyl	benzyl	H	H	4-hydroxy	H
205	Methyl	methyl	benzyl	H	H	2,6-dimethyl-4-hydroxy	H
207	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
209	H	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
211	Methyl	methyl	phenyl	H	H	4-hydroxy	H
213	H	methyl	phenyl	H	H	4-hydroxy	H
215	Ethyl	methyl	phenyl	H	H	4-hydroxy	H
216	Ethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
218	Benzyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
219	Benzyl	methyl	phenyl	H	H	4-hydroxy	H
224	Isopropyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
225	Isopropyl	methyl	phenyl	H	H	4-hydroxy	H
226	2 Carboxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
227	3-Carboxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
229	2-Bromo-4,5-dimethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
230	2-Carboxy-4,5-dimethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
231	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	H	H

TABLE I-continued

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
232	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl	H
233	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl	H
234	3,4-Dimethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-imidazol-2-yl	H
236	3,4-Dimethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl	H
237	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-chlorophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
238	3-Carboxy, 4-methoxy-phenylmethyl	methyl	4-fluorophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
239	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-chlorophenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
240	4-Carboxy-phenylmethyl	methyl	4-chlorophenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
241	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-chlorophenyl	Cl	H	2,6-dimethyl-4-aminocarbonyl	H
242	3-(1H-tetrazol-5-yl)-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
243	3-Carboxy-4-trifluoromethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
244	Bis-3,4-trifluoromethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
245	3-Carboxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
246	Quinolin-4-yl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
247	4-Methoxy naphthalen-1-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
248	4-Trifluoromethoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
249	4-Trifluoromethyl-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
250	4-Isopropyloxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
251	3-Ethoxyphenyl-methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
252	5-Methoxycarbonyl-pyridin-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
253	5-Carboxy-pyridin-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
254	6-Carboxy-pyridin-3-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
255	6-Methoxycarbonyl-pyridin-3-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
256	5-Carboxy-furan-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
257	5-Methoxycarbonyl-furan-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
258	3,4-Dimethoxy-phenylmethyl	hydroxy methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
259	Benzyl	hydroxy methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
260	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
261	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-hydroxy	H
262	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-hydroxy	H/Me
263	3-Carboxy-4-methoxy-phenylmethyl	H	phenyl	H	H	4-hydroxy	H
264	3-Carboxy-4-methoxy-phenylmethyl	H	phenyl	H	H	4-hydroxy	H/Me
265	3-Carboxy-4-methoxy-phenylmethyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H

TABLE I-continued

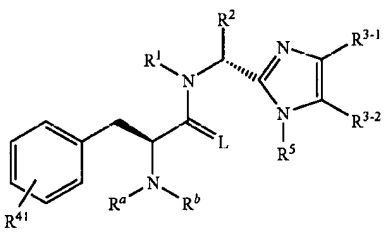
Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
266	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	H	H
267	3-(1H-tetrazol-5-yl)-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
268	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
269	3-Methoxycarbonyl	methyl	phenyl	H	H	4-aminocarbonyl	H
270	3-Carboxy	methyl	phenyl	H	H	4-aminocarbonyl	H
271	3-Methoxycarbonyl	H	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
272	3-Carboxy	H	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
274	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-benzyloxy	H/Me
275	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
277	3-Carboxy-phenyl	methyl	4-chlorophenyl	Me	H	4-aminocarbonyl	H
279	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-hydroxy	H
286	5-Methoxycarbonyl-furan-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
287	5-Carboxy-furan-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
288	3-Carboxy-4-methoxy-phenylmethyl	methyl	3-bromophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
289	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-iodophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
290	3-Carboxy-4-methoxy-phenylmethyl	methyl	2-bromophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
291	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-bromophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
292	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl	H
293	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-chlorophenyl	methyl	H	4-hydroxy	H
295	3-Aminocarbonyl-4-methoxy phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
296	3-(Morpholin-4-ylcarbonyl)-4-methoxy phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
297	-3-Aminocarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-hydroxy	H
298	3-(Morpholin-4-ylcarbonyl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-hydroxy	H
299	3-(2-Hydroxy eth-1-yl-aminocarbonyl)-4-methoxy phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
300	3-(Cyclopropyl aminocarbonyl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H

TABLE I-continued

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
301	3-(Phenylamino carbonyl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
303	5-Methoxycarbonyl-furan-2-ylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
304	5-Carboxy-furan-2-ylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
305	3-(Phenylamino carbonyl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
306	3-(3-carboxyphenyl aminocarbonyl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
307	3-(1H-Tetrazol-5-yl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
308	3-(4-Carboxyphenyl aminocarbonyl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
309	3-(2-t-Butyl-tetrazol-5-yl)-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
310	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	Methoxycarbonyl
311	2-Methoxycarbonyl-pyridin-4-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
312	4-Methoxycarbonylpyridin-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
313	6-Methoxycarbonyl-pyridin-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
315	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	Methoxycarbonyl
316	2-Carboxy-pyridin-4-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
317	6-Carboxy-pyridin-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H

Exemplified compounds of the present invention include compounds of Formula (Ic):

Formula (Ic)



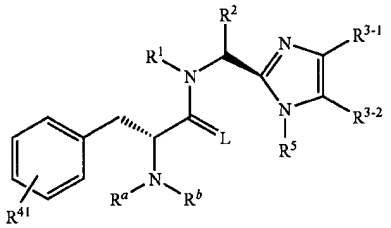
wherein in one embodiment of this invention the variables are as previously defined. In another embodiment of the present invention L is O and R^1, R^2, R^{3-1}, R^{3-2}, R^5, R^a, R^b, and R^{41} are dependently selected from the group consisting of:

TABLE II

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
22	3,4-Dimethoxy-phenylmethyl	benzyloxy methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
63	Isopropyl	hydroxy methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
82	Isopropyl	methyl	4-fluorophenyl	H	H	2,6-dimethyl-4-hydroxy	H
110	2-Phenylethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
113	Benzyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
128	Cyclohexyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
144	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
180	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-(morpholin-4-ylcarbonyl)	H
182	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-ethylamino carbonyl	H
184	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-methylamino carbonyl	H
203	Methyl	methyl	phenyl	H	H	4-aminocarbonyl	H
206	Methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
208	H	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
210	Methyl	methyl	phenyl	H	H	4-hydroxy	H
212	H	methyl	phenyl	H	H	4-hydroxy	H
214	Ethyl	methyl	phenyl	H	H	4-hydroxy	H
217	Ethyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
220	Benzyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
221	Benzyl	methyl	phenyl	H	H	4-hydroxy	H
222	Isopropyl	methyl	phenyl	H	H	4-hydroxy	H
223	Isopropyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
228	3-Carboxy-phenyl methyl	methyl	4-chlorophenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
276	3-Carboxy-phenyl	methyl	4-chlorophenyl	Me	H	4-aminocarbonyl	H
278	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-chlorophenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
280	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
281	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
282	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
283	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
294	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-chlorophenyl	Me	H	4-hydroxy	H
314	6-Methoxycarbonyl-pyridin-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
318	3-Carboxy-4-methoxy-phenylmethyl	methyl	4-chlorophenyl	H	H	4-aminocarbonyl	H

Another embodiment is directed to compositions comprised of a compound of Formula (Id):

Formula (Id)



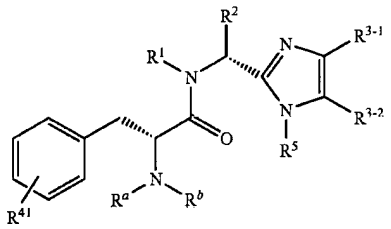
wherein in one embodiment of this invention the variables are as previously defined. In another embodiment of the present invention L is oxygen and R^1, R^2, R^{3-1}, R^{3-2}, R^5, R^a, R^b, and R^{41} are dependently selected from the group consisting of:

TABLE III

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
273	3-Carboxy-4-methoxyphenyl methyl	methyl	phenyl	H	H	4-aminocarbonyl	H

Exemplified compounds of the present invention include compounds of Formula (Ie):

Formula (Ie)



wherein in one embodiment of this invention the variables are as previously defined. In another embodiment of the present invention L is O and R^1, R^2, R^{3-1}, R^{3-2}, R^5, R^a, R^b, and R^{41} are dependently selected from the group consisting of:

TABLE IV

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a/R^b
284	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
285	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H

A further embodiment of the present invention includes representative compounds shown in Table V:

TABLE V

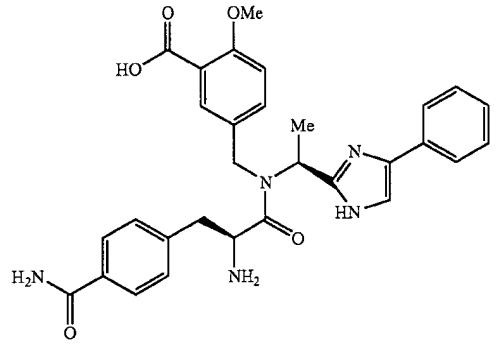
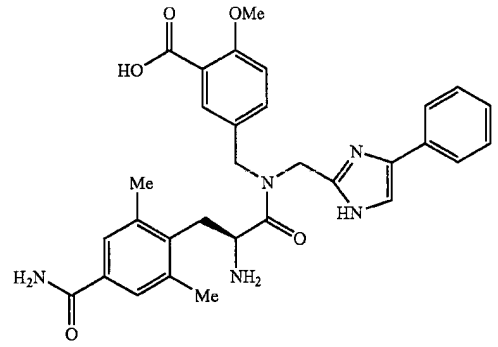
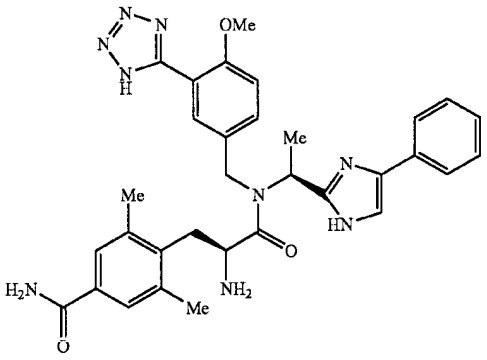
Cpd	
4	

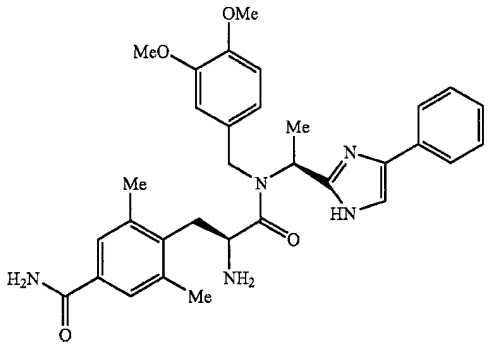
TABLE V-continued

Cpd	
6	

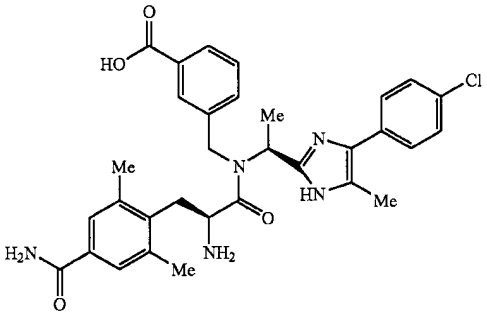
8



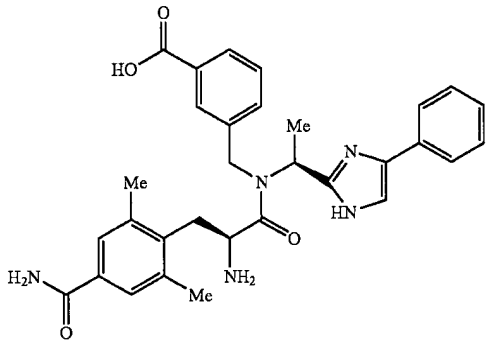
75



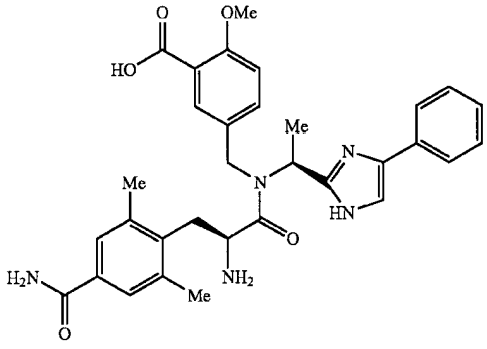
12



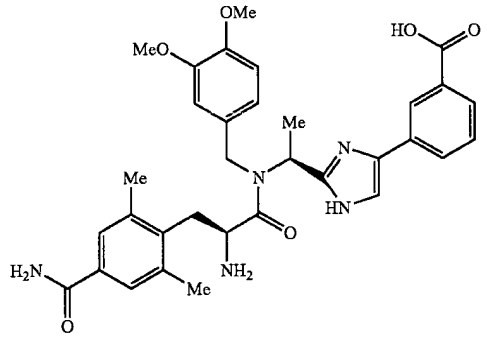
227



18



20



The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts" (*Ref. International J. Pharm.*, 1986, 33, 201-217; *J. Pharm. Sci.*, 1997 (January), 66, 1, 1). Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Representative organic or inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic acid. Representative organic or inorganic bases include, but are not limited to, basic or cationic salts such as benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "*Design of Prodrugs*", ed. H. Bundgaard, Elsevier, 1985.

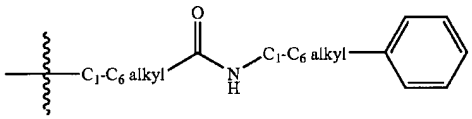
Where the compounds according to this invention have at least one chiral center, they may accordingly exist as enantiomers. Where the compounds possess two or more chiral centers, they may additionally exist as diastereomers. Where

the processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form or as individual enantiomers or diasteromers by either stereospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers or diasteromers by standard techniques, such as the formation of stereoisomeric pairs by salt formation with an optically active acid, such as (−)-di-p-toluoyl-D-tartaric acid and/or (+)-di-p-toluoyl-L-tartaric acid followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of stereoisomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column. It is to be understood that all stereoisomers, racemic mixtures, diastereomers and enantiomers thereof are encompassed within the scope of the present invention.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J. F. W. McOmie, Plenum Press, 1973; and T. W. Greene & P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known in the art.

Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

In general, under standard nomenclature rules used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. Thus, for example, a "phenylC_1-C_6 alkylamidoC_1-C_6alkyl" substituent refers to a group of the formula:



It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

An "independently" selected substituent refers to a group of substituents, wherein the substituents may be different. Therefore, designated numbers of carbon atoms (e.g. C_{1-8}) shall refer independently to the number of carbon atoms in an alkyl or cycloalkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

As used herein, unless otherwise noted, "alkyl" whether used alone or as part of a substituent group refers to straight and branched carbon chains having 1 to 8 carbon atoms or any number within this range. The term "alkoxy" refers to an —Oalkyl substituent group, wherein alkyl is as defined supra. Similarly, the terms "alkenyl" and "alkynyl" refer to straight and branched carbon chains having 2 to 8 carbon atoms or any number within this range, wherein an alkenyl chain has at least one double bond in the chain and an alkynyl chain has at least one triple bond in the chain. An alkyl and alkoxy chain may be substituted on a carbon atom. In substituent groups with multiple alkyl groups such as $(C_{1-6}alkyl)_2$amino- the C_{1-6}alkyl groups of the dialkylamino may be the same or different.

The term "cycloalkyl" refers to saturated or partially unsaturated, monocyclic or polycyclic hydrocarbon rings of from 3 to 14 carbon atom members. Examples of such rings include, and are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and adamantyl. Alternatively, the cycloalkyl ring may be fused to a benzene ring (benzo fused cycloalkyl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen) to form a heteroaryl fused cycloalkyl.

The term "heterocyclyl" refers to a nonaromatic cyclic ring of 5 to 7 members in which 1 to 2 members are nitrogen, or a nonaromatic cyclic ring of 5 to 7 members in which zero, one or two members are nitrogen and up to two members are oxygen or sulfur; wherein, optionally, the ring contains zero to one unsaturated bonds, and, optionally, when the ring is of 6 or 7 members, it contains up to two unsaturated bonds. The term "heterocyclyl" includes a 5 to 7 membered monocyclic heterocyclic ring fused to a benzene ring (benzo fused heterocyclyl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered cycloalkyl or cycloalkenyl ring, a 5 to 7 membered heterocyclyl ring (of the same definition as above but absent the option of a further fused ring) or fused with the carbon of attachment of a cycloalkyl, cycloalkenyl or heterocyclyl ring to form a spiro moiety. For instant compounds of the invention, the carbon atom ring members that form the heterocyclyl ring are fully saturated. Other compounds of the invention may have a partially saturated heterocyclyl ring. The term "heterocyclyl" also includes a 5 to 7 membered monocyclic heterocycle bridged to form bicyclic rings. Such compounds are not considered to be fully aromatic and are not referred to as heteroaryl compounds. Examples of heterocyclyl groups include, and are not limited to, pyrrolinyl (including 2H-pyrrole, 2-pyrrolinyl or 3-pyrrolinyl), pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl.

The term "aryl" refers to an unsaturated, aromatic monocyclic ring of 6 carbon members or to an unsaturated, aromatic polycyclic ring of from 10 to 14 carbon members. Examples of such aryl rings include, and are not limited to, phenyl, naphthalenyl or anthracenyl. Preferred aryl groups for the practice of this invention are phenyl and naphthalenyl.

The term "heteroaryl" refers to an aromatic ring of 5 or 6 members wherein the ring consists of carbon atoms and has at least one heteroatom member. Suitable heteroatoms include nitrogen, oxygen or sulfur. In the case of 5 membered rings, the heteroaryl ring contains one member of nitrogen, oxygen or sulfur and, in addition, may contain up to three additional nitrogens. In the case of 6 membered rings, the heteroaryl ring may contain from one to three nitrogen atoms. For the case wherein the 6 membered ring has three nitrogens, at most two nitrogen atoms are adjacent. Optionally, the heteroaryl ring is fused to a benzene ring (benzo fused heteroaryl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered cycloalkyl ring or a 5 to 7 membered heterocyclo ring (as defined supra but absent the option of a further fused ring).

Examples of heteroaryl groups include, and are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl or pyrazinyl; fused heteroaryl groups include indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, quinolizinyl, quinolinyl, isoquinolinyl or quinazolinyl.

The term "arylalkyl" means an alkyl group substituted with an aryl group (e.g., benzyl, phenethyl). Similarly, the term "arylalkoxy" indicates an alkoxy group substituted with an aryl group (e.g., benzyloxy).

The term "halogen" refers to fluorine, chlorine, bromine and iodine. Substituents that are substituted with multiple halogens are substituted in a manner that provides compounds, which are stable.

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., arylalkyl, alkylamino) it shall be interpreted as including those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., C_1-C_6) shall refer independently to the number of carbon atoms in an alkyl moicty or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root. For alkyl, and alkoxy substituents the designated number of carbon atoms includes all of the independent member included in the range specified individually and all the combination of ranges within in the range specified. For example C_{1-6} alkyl would include methyl, ethyl, propyl, butyl, pentyl and hexyl individually as well as sub-combinations thereof (e.g. C_{1-2}, C_{1-3}, C_{1-4}, C_{1-5}, C_{2-6}, C_{3-6}, C_{4-6}, C_{5-6}, C_{2-5}, etc.).

The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

The novel compounds of the present invention are useful opioid receptor modulators. In particular, certain compounds are opioid receptor agonists useful in the treatment or amelioration of conditions such as pain and gastrointestinal disorders. Examples of pain intended to be within the scope of the present invention include, but are not limited to, centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, pain related to inflammation, progressive disease related pain, neuropathic pain and acute pain such as caused by acute injury, trauma or surgery and chronic pain such as caused by neuropathic pain conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes or cluster or migraine headaches. Examples of gastrointestinal disorders intended to be within the scope of this invention include, but are not limited to, diarrheic syndromes, motility disorders such as diarrhea-predominant, or alternating irritable bowel syndrome, and visceral pain and diarrhea associated with inflammatory bowel disease including ulcerative colitis and Crohn's disease.

Examples of gastrointestinal disorders where opioid receptor ("OR") antagonists are useful include constipation-predominant irritable bowel syndrome, post-operative ileus and constipation, including but not limited to the constipation associated with treatment of chronic pain with opiates. Modulation of more than one opioid receptor subtype is also useful as follows: a compound that is a mixed mu OR agonist and delta OR antagonist could have antidiarrheal properties without being profoundly constipating. A compound that is a mixed mu OR agonist and delta OR agonist are useful in cases of severe diarrhea that are refractory to treatment with pure mu OR agonists, or has additional utility in treating visceral pain associated with inflammation and diarrhea.

Accordingly, a compound of the present invention may be administered by any conventional route of administration including, but not limited to oral, nasal, pulmonary, sublingual, ocular, transdermal, rectal, vaginal and parenteral (i.e. subcutaneous, intramuscular, intradermal, intravenous etc.). It is currently preferred that the compounds of the present invention be administered via modes of administration other than pulmonary or parenteral administration. However, the preferred compounds provided in Table IV may be administered via pulmonary or parenteral modes of administration.

To prepare the pharmaceutical compositions of this invention, one or more compounds of Formula (I) or salt thereof as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable carriers are well known in the art. Descriptions of some of these pharmaceutically acceptable carriers may be found in *The Handbook of Pharmaceutical Excipients*, published by the American Pharmaceutical Association and the Pharmaceutical Society of Great Britain.

Methods of formulating pharmaceutical compositions have been described in numerous publications such as *Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded*, Volumes 1-3, edited by Lieberman et al; *Pharmaceutical Dosage Forms: Parenteral Medications*, Volumes 1-2, edited by Avis et al; and *Pharmaceutical Dosage Forms: Disperse Systems*, Volumes 1-2, edited by Lieberman et al; published by Marcel Dekker, Inc.

In preparing a pharmaceutical composition of the present invention in liquid dosage form for oral, topical and parenteral administration, any of the usual pharmaceutical media or excipients may be employed. Thus, for liquid dosage forms, such as suspensions (i.e. colloids, emulsions and dispersions) and solutions, suitable carriers and additives include, but are not limited to, pharmaceutically acceptable wetting agents, dispersants, flocculation agents, thickeners, pH control agents (i.e. buffers), osmotic agents, coloring agents, flavors, fragrances, preservatives (i.e. to control microbial growth, etc.) and a liquid vehicle may be employed. Not all of the components listed above will be required for each liquid dosage form.

In solid oral preparations such as, for example, dry powders for reconstitution or inhalation, granules, capsules, caplets, gelcaps, pills and tablets (each including immediate release, timed release and sustained release formulations), suitable carriers and additives include but are not limited to diluents, granulating agents, lubricants, binders, glidants, disintegrating agents and the like. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated, gelatin coated, film coated or enteric coated by standard techniques.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, of from about 0.01 mg/kg to about 300

mg/kg (preferably from about 0.01 mg/kg to about 100 mg/kg; and, more preferably, from about 0.01 mg/kg to about 30 mg/kg) and may be given at a dosage of from about 0.01 mg/kg/day to about 300 mg/kg/day (preferably from about 0.01 mg/kg/day to about 100 mg/kg/day and more preferably from about 0.01 mg/kg/day to about 30 mg/kg/day). Preferably, the method for the treatment of conditions that may be mediated by opioid receptors described in the present invention using any of the compounds as defined herein, the dosage form will contain a pharmaceutically acceptable carrier containing between from about 0.01 mg to about 100 mg; and, more preferably, from about 5 mg to about 50 mg of the compound, and may be constituted into any form suitable for the mode of administration selected. The dosages, however, may be varied depending upon the requirement of the subjects, the severity of the condition being treated and the compound being employed. The use of either daily administration or post-periodic dosing may be employed.

Preferably these compositions are in unit dosage forms from such as tablets, pills, capsules, dry powders for reconstitution or inhalation, granules, lozenges, sterile solutions or suspensions, metered aerosol or liquid sprays, drops, or suppositories for administration by oral, intranasal, sublingual, intraocular, transdermal, rectal, vaginal, dry powder inhaler or other inhalation or insufflation means.

For preparing solid pharmaceutical compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as diluents, binders, adhesives, disintegrants, lubricants, antiadherents and gildants. Suitable diluents include, but are not limited to, starch (i.e. corn, wheat, or potato starch, which may be hydrolized), lactose (granulated, spray dried or anhydrous), sucrose, sucrose-based diluents (confectioner's sugar; sucrose plus about 7 to 10 weight percent invert sugar; sucrose plus about 3 weight percent modified dextrins; sucrose plus invert sugar, about 4 weight percent invert sugar, about 0.1 to 0.2 weight percent cornstarch and magnesium stearate), dextrose, inositol, mannitol, sorbitol, microcrystalline cellulose (i.e. AVICEL™ microcrystalline cellulose available from FMC Corp.), dicalcium phosphate, calcium sulfate dihydrate, calcium lactate trihydrate and the like. Suitable binders and adhesives include, but are not limited to acacia gum, guar gum, tragacanth gum, sucrose, gelatin, glucose, starch, and cellulosics (i.e. methylcellulose, sodium carboxymethylcellulose, ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, and the like), water soluble or dispersible binders (i.e. alginic acid and salts thereof, magnesium aluminum silicate, hydroxyethylcellulose [i.e. TYLOSE™ available from Hoechst Celanese], polyethylene glycol, polysaccharide acids, bentonites, polyvinylpyrrolidone, polymethacrylates and pregelatinized starch) and the like. Suitable disintegrants include, but are not limited to, starches (corn, potato, etc.), sodium starch glycolates, pregelatinized starches, clays (magnesium aluminum silicate), celluloses (such as crosslinked sodium carboxymethylcellulose and microcrystalline cellulose), alginates, pregelatinized starches (i.e. corn starch, etc.), gums (i.e. agar, guar, locust bean, karaya, pectin, and tragacanth gum), crosslinked polyvinylpyrrolidone and the like. Suitable lubricants and antiadherents include, but are not limited to, stearates (magnesium, calcium and sodium), stearic acid, talc waxes, stearowet, boric acid, sodium chloride, DL-leucine, carbowax 4000, carbowax 6000, sodium oleate, sodium benzoate, sodium acetate, sodium lauryl sulfate, magnesium lauryl sulfate and the like. Suitable gildants include, but are not limited to, talc, cornstarch, silica (i.e. CAB-O-SIL™ silica available from Cabot, SYLOID™ silica available from W.R. Grace/Davison, and AEROSIL™ silica available from Degussa) and the like. Sweeteners and flavorants may be added to chewable solid dosage forms to improve the palatability of the oral dosage form. Additionally, colorants and coatings may be added or applied to the solid dosage form for ease of identification of the drug or for aesthetic purposes. These carriers are formulated with the pharmaceutical active to provide an accurate, appropriate dose of the pharmaceutical active with a therapeutic release profile.

Generally these carriers are mixed with the pharmaceutical active to form a solid preformulation composition containing a homogeneous mixture of the pharmaceutical active of the present invention, or a pharmaceutically acceptable salt thereof. Generally the preformulation will be formed by one of three common methods: (a) wet granulation, (b) dry granulation and (c) dry blending. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from about 0.1 mg to about 500 mg of the active ingredient of the present invention. The tablets or pills containing the novel compositions may also be formulated in multilayer tablets or pills to provide a sustained or provide dual-release products. For example, a dual release tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer, which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric materials such as shellac, cellulose acetate (i.e. cellulose acetate phthalate, cellulose acetate trimetllitate), polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, methacrylate and ethylacrylate copolymers, methacrylate and methyl methacrylate copolymers and the like. Sustained release tablets may also be made by film coating or wet granulation using slightly soluble or insoluble substances in solution (which for a wet granulation acts as the binding agents) or low melting solids a molten form (which in a wet granulation may incorporate the active ingredient). These materials include natural and synthetic polymers waxes, hydrogenated oils, fatty acids and alcohols (i.e. beeswax, carnauba wax, cetyl alcohol, cetylstearyl alcohol, and the like), esters of fatty acids metallic soaps, and other acceptable materials that can be used to granulate, coat, entrap or otherwise limit the solubility of an active ingredient to achieve a prolonged or sustained release product.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, but are not limited to aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable suspending agents for aqueous suspensions, include synthetic and natural gums such as, acacia, agar, alginate (i.e. propylene alginate, sodium alginate and the like), guar, karaya, locust bean, pectin, tragacanth, and xanthan gum, cellulosics such as sodium carboxymethylcellulose, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose and hydroxypropyl methylcellulose, and combinations thereof, synthetic polymers such as polyvinyl pyrrolidone,

carbomer (i.e. carboxypolymethylene), and polyethylene glycol; clays such as bentonite, hectorite, attapulgite or sepiolite; and other pharmaceutically acceptable suspending agents such as lecithin, gelatin or the like. Suitable surfactants include but are not limited to sodium docusate, sodium lauryl sulfate, polysorbate, octoxynol-9, nonoxynol-10, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polyoxamer 188, polyoxamer 235 and combinations thereof. Suitable deflocculating or dispersing agent include pharmaceutical grade lecithins. Suitable flocculating agent include but are not limited to simple neutral electrolytes (i.e. sodium chloride, potassium, chloride, and the like), highly charged insoluble polymers and polyelectrolyte species, water soluble divalent or trivalent ions (i.e. calcium salts, alums or sulfates, citrates and phosphates (which can be used jointly in formulations as pH buffers and flocculating agents). Suitable preservatives include but are not limited to parabens (i.e. methyl, ethyl, n-propyl and n-butyl), sorbic acid, thimerosal, quaternary ammonium salts, benzyl alcohol, benzoic acid, chlorhexidine gluconate, phenylethanol and the like. There are many liquid vehicles that may be used in liquid pharmaceutical dosage forms, however, the liquid vehicle that is used in a particular dosage form must be compatible with the suspending agent(s). For example, nonpolar liquid vehicles such as fatty esters and oils liquid vehicles are best used with suspending agents such as low HLB (Hydrophile-Lipophile Balance) surfactants, stearalkonium hectorite, water insoluble resins, water insoluble film forming polymers and the like. Conversely, polar liquids such as water, alcohols, polyols and glycols are best used with suspending agents such as higher HLB surfactants, clays silicates, gums, water soluble cellulosics, water soluble polymers and the like.

Furthermore, compounds of the present invention can be administered in an intranasal dosage form via topical use of suitable intranasal vehicles or via transdermal skin patches, the composition of which are well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the administration of a therapeutic dose will, of course, be continuous rather than intermittent throughout the dosage regimen.

Compounds of this invention may be administered in any of the foregoing compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever treatment of disorders that may be mediated or ameliorated by opioid receptors for a subject in need thereof.

The daily dose of a pharmaceutical composition of the present invention may be varied over a wide range from about 0.1 mg to about 7000 mg per adult human per day; most preferably the dose will be in the range of from about 0.7 mg to about 2100 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the subject to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 300 mg/kg of body weight per day. Preferably, the range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day; and, most preferably, from about 0.01 mg/kg to about 30 mg/kg of body weight per day. Advantageously, a compound of the present invention may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, and the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject age, weight, diet and time of administration, will result in the need to adjust the dose to an appropriate therapeutic level.

Representative IUPAC names for the compounds of the present invention were derived using the AutoNom version 2.1 nomenclature software program provided by Beilstein Informationssysteme.

Abbreviations used in the instant specification, particularly the Schemes and Examples, are as follows:

BOC =	tert-butoxycarbonyl
BuLi =	n-butyllithium
CBZ =	benzyloxycarbonyl
Cpd or Cmpd =	compound
d =	day/days
DIPEA =	diisopropylethylamine
DPPF =	1,1'-bis(diphenylphosphino)ferrocene
DPPP =	1,3-Bis(diphenylphosphino)propane
EDCI or EDC =	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
EtOAc =	ethyl acetate
EtOH =	ethanol
h =	hour/hours
HMDS =	1,1,3,3-Hexamethyldisilazane
HOBt/HOBT =	hydroxybenzotiazole
M =	molar
MeCN =	acetonitrile
MeOH =	methanol
min =	minutes
PyBOP =	Benzotriazol-1-yl-oxy-tris-pyrrolidinophosphonium hexafluorophosphate
rt/RT =	room temperature
TFA =	trifluoroacetic acid
OTf =	triflate
Ts =	tosyl

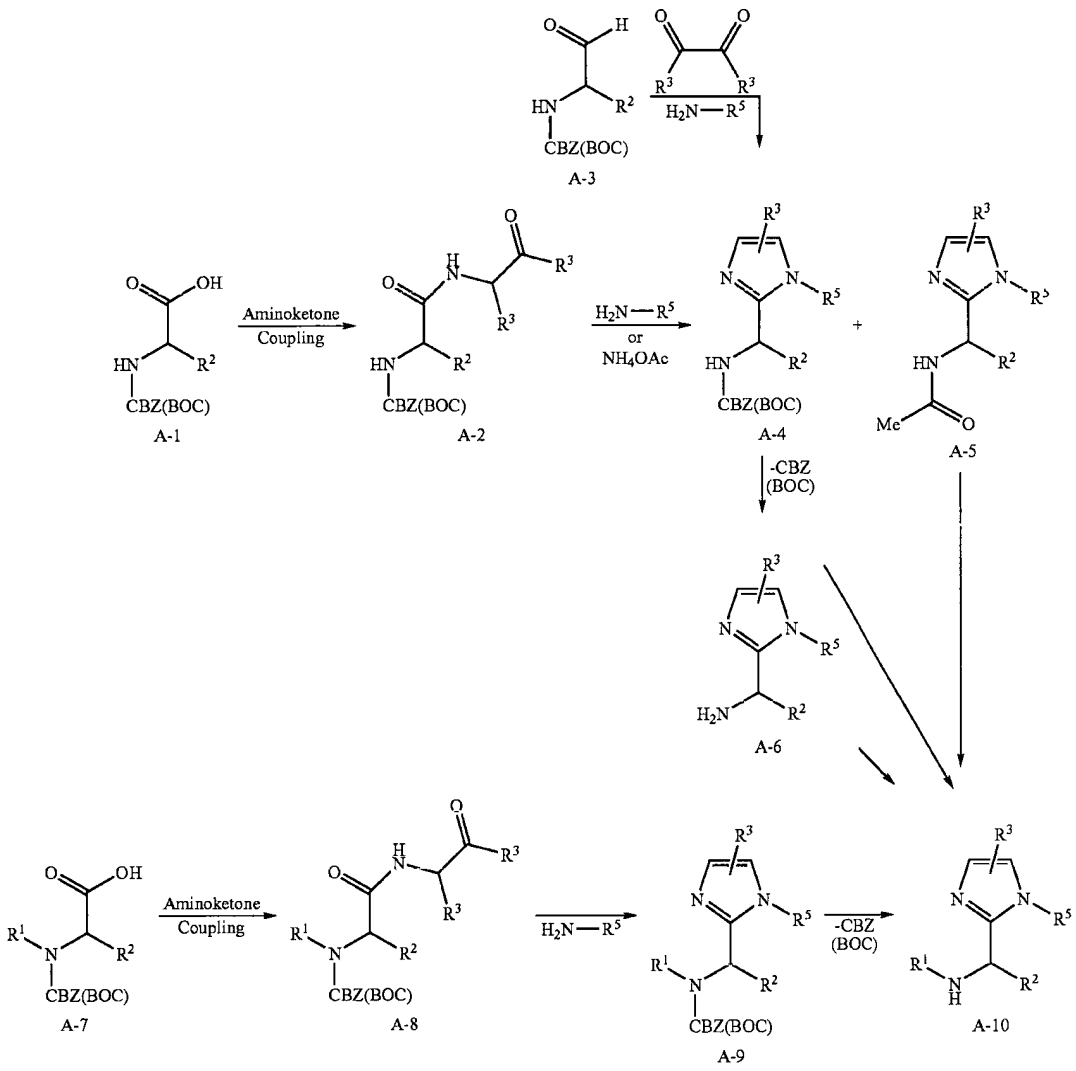
Synthetic Methods

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the schemes that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art.

The following schemes describe general synthetic methods whereby intermediate and target compounds of the present invention may be prepared. Additional representative compounds and stereoisomers, racemic mixtures, diasteromers and enantiomers thereof can be synthesized using the intermediates prepared in accordance to the general schemes and other materials, compounds and reagents known to those skilled in the art. All such compounds, stereoisomers, racemic mixtures, diasteromers and enantiomers thereof are intended to be encompassed within the scope of the present invention.

Certain intermediates and compounds of the present invention may be prepared according to the process outlined in Scheme A below.

Scheme A



A carboxylic acid of the formula A-1, available either commercially or prepared by reported protocols in the scientific literature, may be coupled to an α-aminoketone using standard peptide coupling conditions with a coupling agent such as EDCI and an additive such as HOBt to provide a compound of formula A-2. Compound A-2 may be condensed with an amine of the formula $H_2N—R_5$ or ammonium acetate and cyclized upon heating in acetic acid to a compound of formula A-4.

The protecting group of compound A-4 may be removed using conditions known to those skilled in the art that are appropriate for the particular protecting group to afford a compound of the formula A-6. For instance, hydrogenation in the presence of a palladium catalyst is one method for the removal of a CBZ protecting group, whereas treatment with an acid such as TFA is effective for a BOC group deprotection.

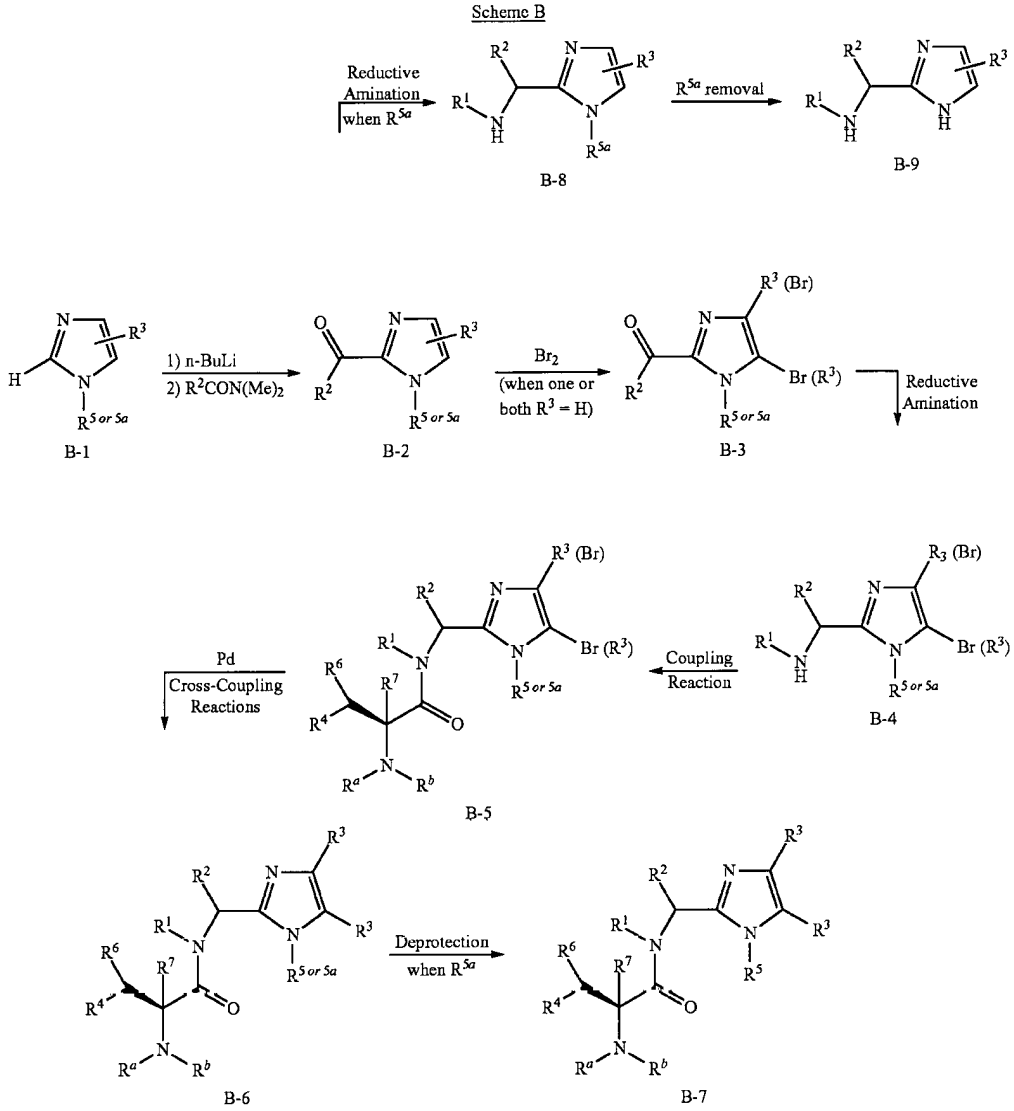
A compound of formula A-6 may be substituted using reductive amination with an appropriately substituted aldehyde or ketone in the presence of a hydride source, such as sodium borohydride or sodium triacetoxyborohydride, provide compounds of formula A-10.

Alternatively, a compound of formula A-3 may be condensed with a dicarbonyl compound of the formula $R_3(C{=}O)_2R_3$ and an amine of the formula $H_2N—R_5$ upon heating in acetic acid to afford a compound of the formula A-4. When compound A-3 is protected with a BOC group, a by-product of formula A-5 may be produced. Compounds of formula A-4 or A-5 may be treated with a hydride source such as lithium aluminum hydride to give certain compounds of formula A-10.

Similarly, a compound of formula A-7 may be coupled to an α-aminoketone as described above for compounds of formula A-1 to yield the corresponding compounds of formula A-8. A compound of formula A-8 may then be cyclized in the presence of an amine of formula $H_2N—R_5$ or ammonium acetate and subsequently deprotected as described above to arrive at compounds of formula A-10.

Certain compounds of the present invention may be prepared according to the process outlined in Scheme B below.

Scheme B



R^{5a} = a N-protecting group, more particularly, R^{5a} = SEM, MOM or the like

More specifically, a compound of formula B-1 (wherein the imidazole nitrogen is substituted with R^5, as defined herein, or R^{5a}, a nitrogen protecting group such as SEM, MOM, or the like) may be deprotonated with an organometallic base such as n-butyllithium and then treated with a suitably substituted amide to yield a compound of formula B-2.

Compound B-2 may be brominated to yield a mixture of regioisomers of formula B-3. A compound of formula B-3 may be further elaborated via a reductive amination with an amine of the formula $H_2N—R^1$ in the presence of a hydride source as described in Scheme A to afford a compound of formula B-4.

The amine of a compound of formula B-4 may be coupled with a suitable carboxylic acid under standard peptide coupling conditions with a coupling agent such as EDCI and an additive such as HOBt to yield compounds of formula B-5.

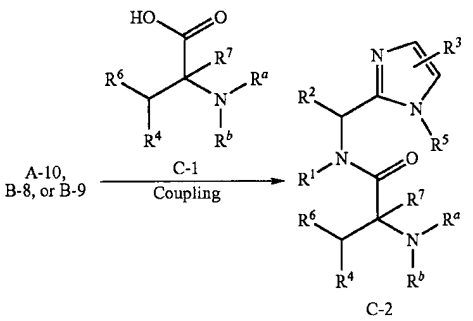
Certain R^3 substituents of the present invention in which a carbon atom is the point of attachment may be introduced into a compound of formula B-5 through a transition metal-catalyzed cross coupling reaction to afford compounds of formula B-6. Suitable palladium catalysts include palladium tetrakis triphenylphosphine and the like. Suitable Lewis acids for the reaction include boronic acids and the like. Compounds protected with R^{5a} may be deprotected under acidic conditions to yield compounds of formula B-7.

In a similar manner, an intermediate B-2 when optionally protected with R^{5a} may be reductively alkylated using methods described above to give a compound of formula B-8, followed by removal of protecting group R^{5a} using conditions described herein to yield a compound of formula B-9.

One skilled in the art will recognize that substituent L (depicted as 0 in the formulae of Scheme B) may be further elaborated to S or N(R^d) of the present invention using conventional, known chemical methods.

Certain compounds of the present invention may be prepared according to the process outlined in Scheme C below.

Scheme C



More specifically, a compound of formula A-10, B-8, or B-9 may be elaborated to a compound of formula C-2 through coupling with a suitable carboxylic acid under standard peptide coupling conditions as described above. One skilled in the art will recognize that substituent L in a compound of formula C-2(depicted as O) may be converted to S or N(R^d) of the present invention using conventional, known chemical methods.

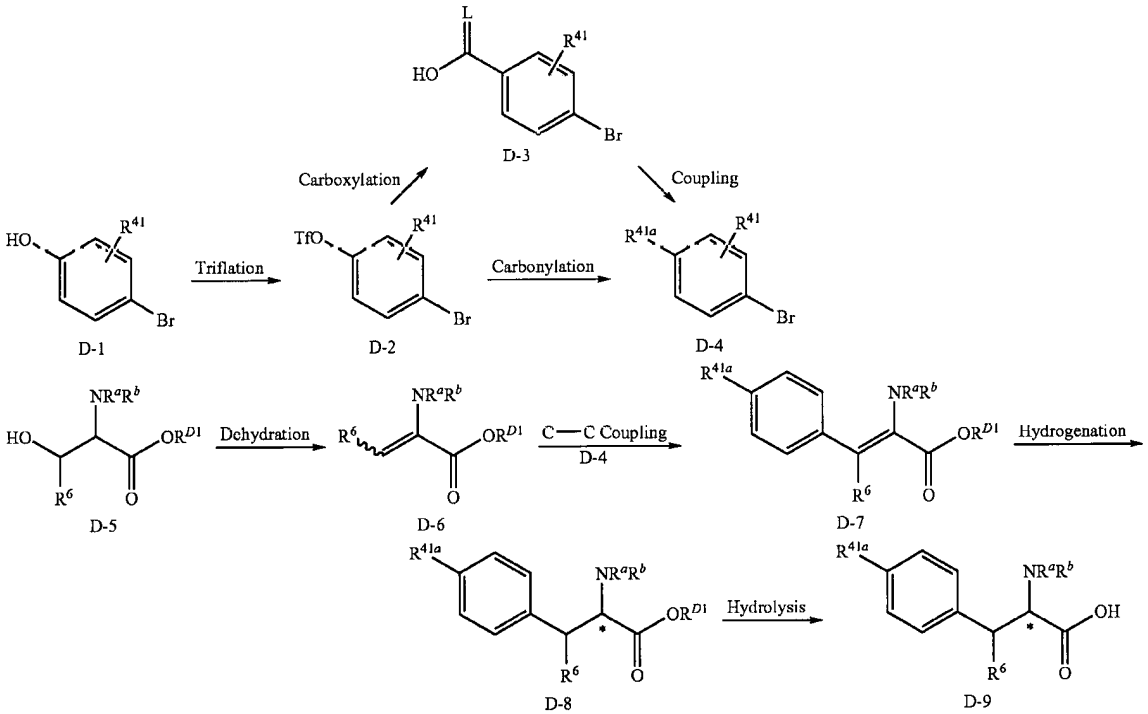
Suitably substituted carboxylic acids of the present invention may either be commercially available or prepared by reported protocols in the scientific literature. Several chemical routes for preparing certain compounds of formula C-1 are outlined below in Schemes D and E.

group of a compound of formula D-2 may undergo a carboxylation reaction via an initial carbonylation under a carbon monoxide atmosphere in the presence of an appropriate palladium catalyst and DPPF, followed by an aqueous basic workup to afford a compound of formula D-3. Subsequently, the carboxyl group may be converted to a substituent of R^{41a} of formula D-4 using standard peptide coupling conditions. Alternatively, a compound of formula D-4 may be directly prepared via a carbonylation of compound of formula D-2, followed by treatment with HMDS, or a primary or secondary amine.

The compound of formula D-5, known or prepared by known methods, may be treated with EDC in the presence of copper (I) chloride to afford the corresponding alkene of formula D6. A compound of formula D-6 may then undergo a Heck reaction with a compound of formula D-4 in the presence of an appropriate palladium catalyst and phosphino ligand to afford a compound of formula D7. Subsequent hydrogenation of the alkenyl substituent using standard hydrogen reduction methods affords a compound of formula D-8.

Scheme E demonstrates an alternative method for preparing intermediate D-7 of the present invention. A compound of formula E-1 may be elaborated to a compound of formula E-4 using the appropriately adapted synthetic steps described in Scheme D. One skilled in the art will recognize that this transformation may be achieved by manipulation of the reaction sequence. A compound of formula E-4 may be converted to its corresponding nitrile via an aromatic nucleophilic displacement reaction with cyanide anion. One skilled in the art will recognize that a nitrile substituent is a viable synthon for a substituent of R^{41a}.

Scheme D

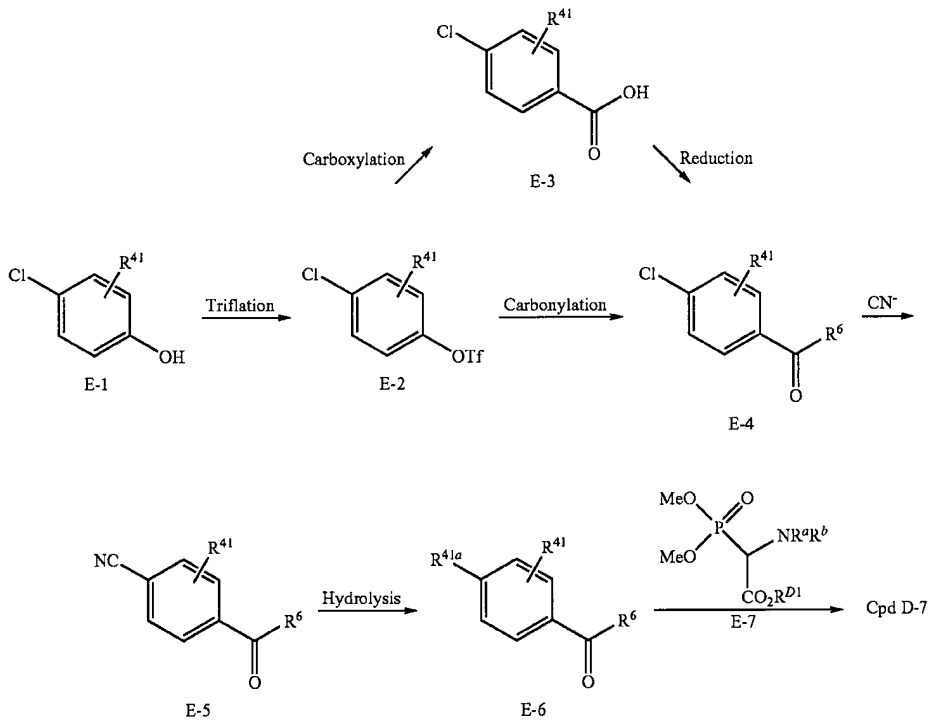


R^{41a} = aminocarbonyl, C_{1-6}alkylaminocarbonyl, or $(C_{1-6}alkyl)_2$aminocarbonyl;
R^{D1} = H, C_{1-6}alkyl, or aryl(C_{1-6}) alkyl

Specifically, a compound of formula D-1 may be treated with trifluoromethanesulfonic anhydride to afford the triflate compound of formula D-2. A compound of formula D-2 may be converted to a compound of formula D-4 by a variety chemical routes which utilize conventional chemical methods known to those skilled in the art. For example, the bromo

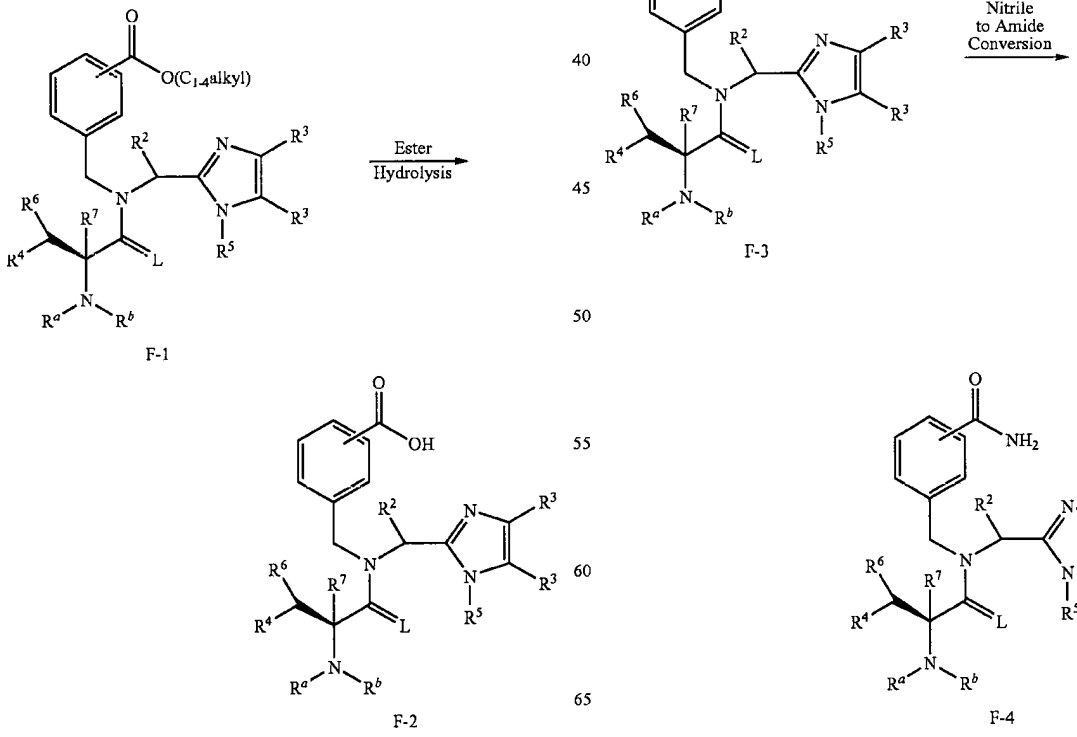
A compound of formula E-4 may participate in a Horner-Wadsworth-Emmons reaction with a compound of formula E-7 in the presence of an organometallic base such as n-butyllithiium to afford a compound of formula D-7. This intermediate may be further elaborated as described in Scheme D, herein.

Scheme E



Certain compounds of the present invention may be prepared according to the process outlined in Scheme F below.

Scheme F



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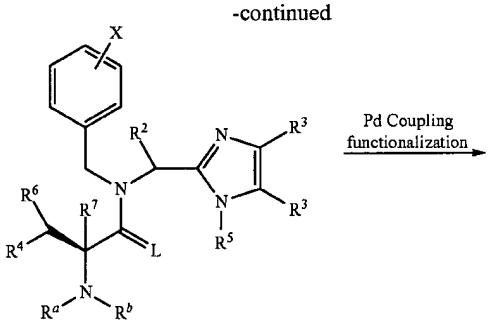
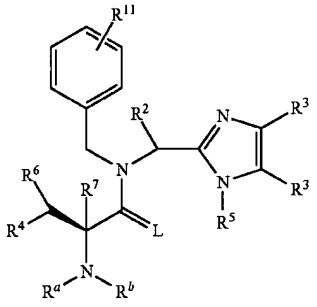


F-5

X = I, Br, —OTs, —OTf



F-6

R^{11} = CN, —CO_2H, -alkoxycarbonyl

More specifically, a compound of formula F-1, wherein R^{11} is an alkoxycarbonyl as defined above, may be saponified to its corresponding acid, a compound of formula F-2.

A compound of formula F-3 wherein R^{11} is a cyano substituent may be elaborated to its corresponding aminocarbonyl, compound F-4 by treatment with hydrogen peroxide in the presence of hydroxide anion. Similarly, when R^3 is a cyano-substituted aryl ring, it may be treated as described above to form an aminocarbonyl-substituted aryl ring.

Certain substitutents of R^{11} may be installed via a palladium catalyzed coupling reaction with an X-substituted precursor. For example, a compound of formula F-5 wherein X is iodide, bromide, tosylate, triflate, or the like may be treated with $Zn(CN)_2$ in the presence of palladium tetrakis triphenylphosphine to give a compound of formula F-6 wherein R^{11} is cyano.

Treatment of a compound of formula F-5 with $Pd(OAc)_2$ and a ligand such as 1,1-bis(diphenylphosphino) ferrocene under a carbon monoxide atmosphere provides a compound of formula F-6 wherein R^{11} is a carboxy substituent.

The palladium catalyzed couplings described above may also be used to install cyano, carboxy, and alkoxycarbonyl substituents onto an aryl ring at R^3.

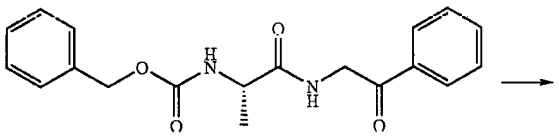
SPECIFIC EXAMPLES

Specific compounds which are representative of this invention were prepared as per the following examples and reaction sequences; the examples and the diagrams depicting the reaction sequences are offered by way of illustration, to aid in the understanding of the invention and should not be construed to limit in any way the invention set forth in the claims which follow thereafter. The instant compounds may also be used as intermediates in subsequent examples to produce additional compounds of the present invention. No attempt has been made to optimize the yields obtained in any of the reactions. One skilled in the art would know how to increase such yields through routine variations in reaction times, temperatures, solvents and/or reagents.

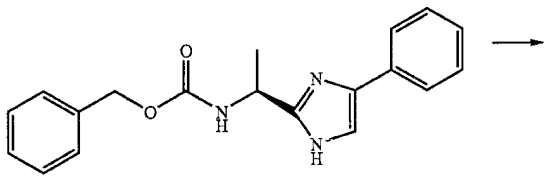
Reagents were purchased from commercial sources. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with (TMS) as the internal standard on a Bruker Biospin, Inc. DPX-300 (300 MHz) spectrometer. The values are expressed in parts per million down field from TMS. The mass spectra (MS) were determined on a Micromass Platform LC spectrometer or an Agilent LC spectrometer using electrospray techniques. Microwave accelerated reactions were performed using either a CEM Discover or a Personal Chemistry Smith Synthesizer microwave instrument. Stereoisomeric compounds may be characterized as racemic mixtures or as separate diastereomers and enantiomers thereof using X-ray crystallography and other methods known to one skilled in the art. Unless otherwise noted, the materials used in the examples were obtained from readily available commercial suppliers or synthesized by standard methods known to one skilled in the art of chemical synthesis. The substituent groups, which vary between examples, are hydrogen unless otherwise noted.

Example 1

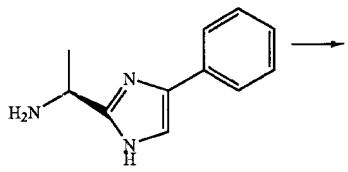
2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-N-isopropyl-N-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-propionamide



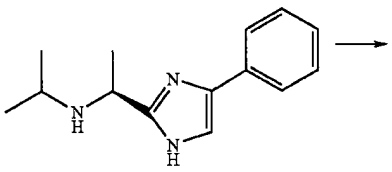
1a



1b



1c



1d

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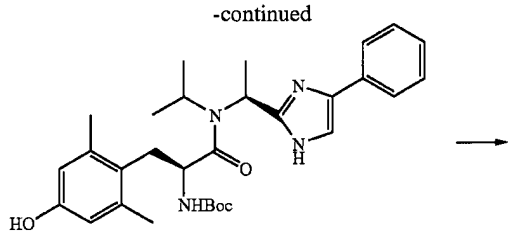
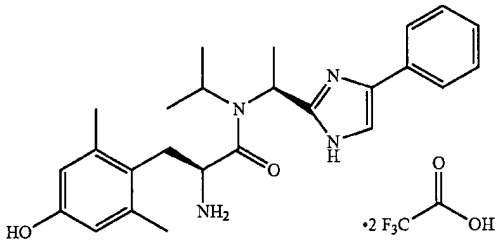


1e



1f

A. [1-(2-Oxo-2-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzyl ester. To a solution of commercially available N-α-CBZ-L-alanine (2.11 g, 9.5 mmol) in dichloromethane (50 mL) was added 2-aminoacetophenone hydrochloride (1.62 g, 9.5 mmol). The resulting solution was cooled to 0° C. and N-methylmorpholine (1.15 g, 11 mmol), 1-hydroxybenzotriazole (2.55 g, 18.9 mmol) and 1[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.35 g, 12.3 mmol) in that order were added under an Argon atmosphere. The reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution; the separated organic phase was washed with 2N citric acid, saturated $NaHCO_3$ solution and brine, then dried over $MgSO_4$ overnight. After filtration and concentration, the residue was purified by column chromatography on silica gel (eluent, EtOAc:hexane-1:1) to give the pure product: [1-(2-oxo-2-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzyl ester (2.68 g, 83%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (3H, d), 4.39 (1H, m), 4.75 (2H, d), 5.13 (2H, d), 5.40 (1H, m), 7.03 (1H, m), 7.36 (5H, m), 7.50 (2H, m), 7.63 (1H, m), 7.97 (2H, m). MS (ES^+): 341.1 (100%).

B. [1-(4-Phenyl-1H-imidazol-2-yl)-ethyl]-carbamic acid benzyl ester. To a suspension of [1-(2-oxo-2-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzyl ester (2.60 g, 7.64 mmol) in xylene (60 mL) was added NH_4OAc (10.3 g, 134 mmol) and HOAc (5 mL). The resulting mixture was heated at reflux for 7 h. After being cooled to room temperature, brine was added and the mixture was separated. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over Na_2SO_4 overnight. After filtration and concentration, the residue was purified by column chromatography on silica gel (eluent, EtOAc:hexane-1:1) to give the title compound (2.33 g, 95%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.65 (3H, d), 5.06 (1H, m), 5.14 (2H, q), 5.94 (1H, d), 7.32 (10H, m), 7.59 (2H, d). MS (ES^+): 322.2 (100%).

C. 1-(4-Phenyl-1H-imidazol-2-yl)-ethylamine. To a solution of [1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamic acid benzyl ester (1.5 g, 4.67 mmol) in methanol (25 mL) was added 10% palladium on carbon (0.16 g). The mixture was shaken in a hydrogenation apparatus at rt under a hydrogen atmosphere (10 psi) for 8 h. Filtration followed by evaporation to dryness under reduced pressure gave the crude product 1-(4-Phenyl-1H-imidazol-2-yl)-ethylamine (0.88 g, 100%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.53 (3H, d), 4.33 (1H, q), 7.23 (3H, m), 7.37 (2H, m), 7.67 (2H, m). MS (ES^+): 188.1 (38%).

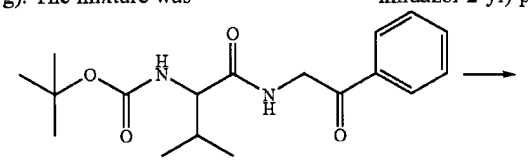
D. Isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amine. 1-(4-Phenyl-1H-imidazol-2-yl)-ethylamine (0.20 g, 1.07 mmol) and acetone (0.062 g, 1.07 mmol) were mixed in 1,2-dichloroethane (4 mL), followed by the addition of $NaBH(OAc)_3$ (0.34 g, 1.61 mmol). The resulting mixture was stirred at rt for 3 h. The reaction was quenched with saturated $NaHCO_3$ solution. The mixture was extracted with EtOAc and the combined extracts were dried over Na_2SO_4. Filtration followed by evaporation to dryness under reduced pressure gave the crude isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amine (0.23 g, 100%) which was used for the next reaction without further purification. ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, d), 1.18 (3H, d), 1.57 (3H, d), 2.86 (1H, m), 4.32 (1H, m), 7.24 (2H, m), 7.36 (2H, m), 7.69 (2H, m). MS (ES^+): 230.2 (100%).

E. (2-(4-Hydroxy-2,6-dimethyl-phenyl)-1-{isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl}-ethyl)-carbamic acid tert-butyl ester. Into a solution of 2-tert-Butoxycarbonylamino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid (0.18 g, 0.6 mmol) in DMF (7 mL) was added isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amine (0.11 g, 0.5 mmol), 1-hydroxybenzotriazole (0.22 g, 1.6 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.12 g, 0.6 mmol). The resulting mixture was stirred under an Argon atmosphere at rt overnight. The reaction mixture was extracted with EtOAc and the combined organic extracts were washed sequentially with saturated aqueous $NaHCO_3$ solution, 1N HCl, saturated aqueous $NaHCO_3$ solution, and brine. The organic phase was then dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (eluent: EtOAc) to afford the product (2-(4-hydroxy-2,6-dimethyl-phenyl)-1-{isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl}-ethyl)-carbamic acid tert-butyl ester (0.13 g, 50%). MS (ES^+): 521.5 (100%).

F. 2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-N-isopropyl-N-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-propionamide. A solution of (2-(4-hydroxy-2,6-dimethyl-phenyl)-1-{isopropyl-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl}-ethyl)-carbamic acid tert-butyl ester (0.13 g, 0.25 mmol) in trifluoroacetic acid (5 mL) was stirred at rt for 2 h. Upon removal of the solvents, the residue was purified by preparative LC and lyophilized to give the TFA salt of the title compound as a white powder (0.042 g). ^1H NMR (300 MHz, $CDCl_3$): δ 0.48 (3H, d), 1.17 (3H, d), 1.76 (3H, d), 2.28 (6H, s), 3.19 (2H, m), 3.74 (1H, m), 4.70 (1H, m), 4.82 (1H, q), 6.56 (2H, s), 7.45 (4H, m), 7.74 (2H, m). MS (ES^+): 421.2 (100%).

Example 2

Methyl-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]amine and Ethyl-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-amine



2a

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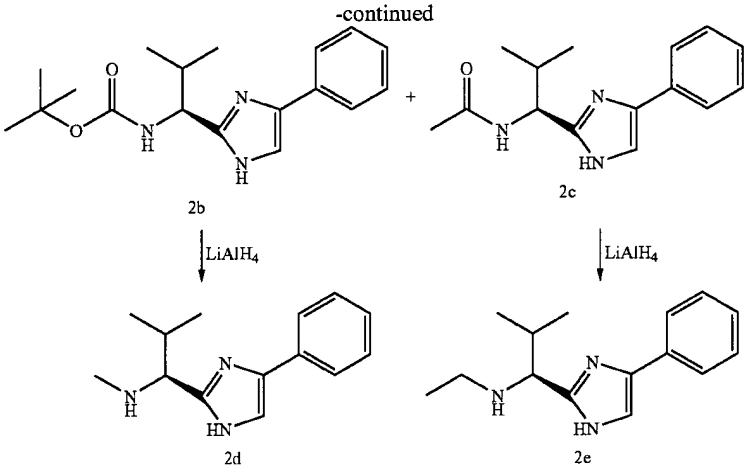


A. [2-Methyl-1-(2-oxo-2-phenyl-ethylcarbamoyl)-propyl]carbamic acid tert-butyl ester. Compound 2a was prepared according to Example 1 using the appropriate reagents, starting materials and methods known to those skilled in the art.

B. [2-Methyl-1-(4-phenyl-1-H-imidazol-2-yl)-propyl]-carbamic acid tert-butyl ester. Following the procedure described in Example 1 for the conversion of Compound 1a to Compound 1b, and using the appropriate reagents and methods known to those skilled in the art, [2-methyl-1-(4-phenyl-1-H-imidazol-2-yl)-propyl]-carbamic acid tert-butyl ester, Cpd 2b, was prepared.

Subsequent to workup, the crude product mixture was subjected to flash silica gel chromatography (eluents: CH_2Cl_2, followed by 4:1 CH_2Cl_2/Et_2O, then EtOAc). Processing of the fractions afforded 1.08 g (27%) of recovered [2-methyl-1-(2-oxo-2-phenyl-ethylcarbamoyl)-propyl]-carbamic acid tert-butyl ester (Cpd 2a), 1.89 g (50%) of [2-methyl-1-(4-phenyl-1-H-imidazol-2-yl)-propyl]-carbamic acid tert-butyl ester (Cpd 2b), and 0.60 g of a mixture of N-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-acetamide (Cpd 2c) and acetamide.

Cpd 2c was purified by dissolving it in hot CH_3CN and cooling to 0° C. Collection of the precipitate by suction filtration afforded 0.21 g (7%) of N-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-acetamide, Cpd 2c, as a white powder (HPLC: 100% @ 254 nm and 214 nm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (2H, br s), 7.33 (2H, t, J=7.5 Hz), 7.25-7.18 (2H, m), 4.78 (1H, br s), 2.35 (1H, br m), 2.02 (3H, s), 1.03 (3H, d, J=6.7 Hz), 0.87 (3H, d, J=6.7 Hz); MS (ES^+) (relative intensity): 258.3 (100) (M+1).

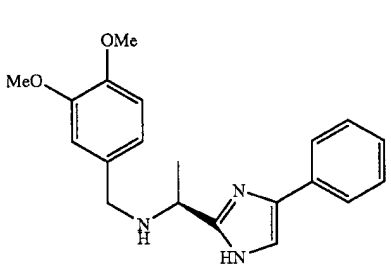
C. Methyl-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]amine. A solution of [2-methyl-1-(4-phenyl-1-H-imidazol-2-yl)-propyl]carbamic acid tert-butyl ester (0.095 g, 0.30 mmol) in THF (2.0 mL) was added dropwise over 10 min to a refluxing 1.0 M solution of $LiAlH_4$ in THF (3.0 mL). The reaction was maintained at reflux for 2 h, cooled to room temperature, and quenched by sequential treatment with 0.11 mL of cold water (5° C.), 0.11 mL of 15% NaOH in aqueous solution, and 0.33 mL of cold water (5° C.). The resultant solid was removed by suction filtration and the filtrate (pH 8-9) was extracted three times with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated to afford 0.58 g (84%) of methyl-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-amine as a light yellow oil (HPLC: 97% @ 254 nm and 214 nm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 (2H, d, J=7.4 Hz), 7.36 (2H, t, J=7.6 Hz), 7.26 (1H, s), 7.25-7.20 (1H, m), 3.62 (1H, d, J=6.3 Hz), 2.35 (3H, s), 2.06 (1H, m), 0.99 (3H, d, J=6.7 Hz), 0.89 (3H, d, J=6.7 Hz); MS (ES^+) (relative intensity): 230.2 (100) (M+1).

D. Ethyl-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-amine. A solution of N-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-acetamide (0.077 g, 0.30 mmol) in THF (2.0 mL) was added dropwise over 10 min to a refluxing 1.0 M solution of $LiAlH_4$ in THF (3.0 mL). The reaction was maintained at reflux for 11 h, cooled to rt, and quenched by sequential treatment with 0.11 mL of cold water (5° C.), 0.11 mL of 15% NaOH in aqueous solution, and 0.33 mL of cold water (5° C.). The resultant solid was removed by suction filtration and the filtrate (pH 8-9) was extracted three times with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated to afford 0.069 g of a 5:1 mixture (determined by ^{1}H NMR) of ethyl-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-amine and recovered Cpd 2c as a colorless oil (HPLC: peaks overlap). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (2H, br s), 7.35 (2H, t, J=7.6 Hz), 7.26-7.17 (2H, m), 3.72 (1H, d, J=6.0 Hz), 2.56 (2H, dq, J=13.0, 7.1 Hz), 2.05 (1H, m), 1.08 (3H, t, J=7.1 Hz), 0.97 (3H, d, J=6.7 Hz), 0.89 (3H, d, J=6.7 Hz); MS (ES^+) (relative intensity): 244.2 (100) (M+1). This sample was of sufficient quality to use in the next reaction without further purification.

Methyl-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-amine and ethyl-[2-methyl-1-(4-phenyl-1H-imidazol-2-yl)-propyl]-amine may be substituted for Cpd 1d of Example 1 and elaborated to compounds of the present invention with the appropriate reagents, starting materials and purification methods known to those skilled in the art.

Example 3

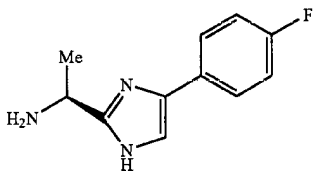
(3,4-Dimethoxy-benzyl)-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amine



A solution of 1-(4-phenyl-1H-imidazol-2-yl)-ethylamine (0.061 g, 0.33 mmol) of Example 1, and 0.55 g (0.33 mmol) of 3,4-dimethoxybenzaldehyde in 5 mL of anhydrous methanol was stirred at room temperature for 1 h and then cooled to about 0-10° C. in an ice bath for 1 h. The reaction was treated carefully with 0.019 g (0.49 mmol) of sodium borohydride in one portion and maintained at about 0-10° C. for 21 h. Cold 2M aqueous HCl was added dropwise (30 drops), the mixture was stirred for 5 min, and then partially concentrated in vacuo unheated. The residual material was taken up in EtOAc to yield a suspension that was treated with 5 mL of cold 3M aqueous NaOH and stirred vigorously until clear. The phases were separated and the aqueous layer was extracted three times additional with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and concentrated to afford 0.11 g of (3,4-dimethoxy-benzyl)-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amine as a light yellow oil (HPLC: 87% @ 254 nm and 66% @ 214 nm). MS (ES^+) (relative intensity): 338.1 (100) (M+1). This sample was of sufficient quality to use in the next reaction without further purification. The title compound may be substituted for Cpd 1d of Example 1 and elaborated to compounds of the present invention with the appropriate reagents, starting materials and purification methods known to those skilled in the art.

Example 4

1-[4-(4-Fluoro-phenyl)-1H-imidazol-2-yl]-ethylamine

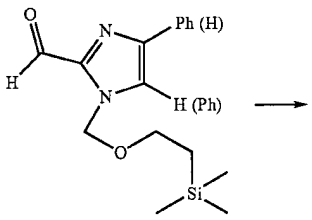


A. {1-[4-(4-Fluoro-phenyl)-1H-imidazol-2-yl]ethyl}-carbamic acid tert-butyl ester. A mixture of ammonium acetate (19.3 g, 250 mmol) and glacial HOAc (35 mL) was stirred mechanically and heated to about 100° C. to give a colorless solution in 5-10 min. After cooling to rt, a solid mixture of N-t-BOC-L-Alaninal (commercially available from Aldrich) and 4-fluorophenyl glyoxal hydrate was added in portions while stirring to give a yellow mixture. The resulting mixture was heated at 100° C. for approximately 2 h before cooling to rt. The mixture was cooled to 0-5° C., then basified by dropwise addition of conc. NH_4OH (25 mL), H_2O (25 mL), and EtOAc (40 mL), and additional conc. NH_4OH (50 mL) to render the mixture alkaline. The phases were separated and the aqueous phase was re-extracted with EtOAc. The combined organic phases were filtered through dicalite to remove an orange solid and were washed with saturated aqueous NaCl. The organic phase was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 4.27 g of an orange-brown residue. The residue was dissolved in a solution of MeCN (22 mL) and DMSO (3 mL) then purified by preparative HPLC on a Kromasil 10 u C18 250x50 mm column, eluting with a 35:65 MeCN:H_2O gradient. The pure fractions were combined and lyophilized to give 1.77 g of the product as a yellow-white powder (42%; TFA salt). MS: m/z 306.1 (MH^+).

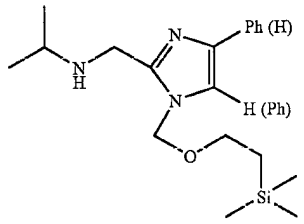
B. 1-[4-(4-Fluoro-phenyl)-1H-imidazol-2-yl]-ethylamine. {1-[4-(4-Fluoro-phenyl)-1H-imidazol-2-yl]-ethyl}-carbamic acid tert-butyl ester may be BOC-deprotected using the procedure described in Example 1 for the conversion of Cpd 1e to Cpd 1f. Upon completion of the BOC-deprotection, the resulting amine may be substituted for Cpd 1c of Example 1 and elaborated to compounds of the present invention with the appropriate reagents, starting materials and purification methods known to those skilled in the art.

Example 5

Isopropyl-[4(5)-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-ylmethyl]-amine (mixture of regioisomers)



5a
Mixture of regioisomers



5b

A. Cpd 5a Regioisomers. Into a cooled solution of 4(5)-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole (*Tet. Lett.* 1986, 27(35), 4095-8) (7.70 g, 28.1 mmol) in dry THF (60 mL) was added n-butyllithium (2.5 M in hexane, 22.5 mL, 56.2 mmol) at −78° C. under N_2. The resulting mixture was stirred at −78° C. for 1 h, followed by the addition of DMF (4.35 mL, 56.2 mmol). After being stirred at −78° C. for an additional hour, the reaction was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4. After filtration and evaporation, the residue was purified by flash column chromatography (eluent: EtOAc:hexane, 1:9) to give 4(5)-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carbaldehyde (5.11 g, 60%) as a mixture of regioisomers. ^1H NMR (300 MHz, $CDCl_3$): δ 0.00 (9H, s), 2.98 (2H, t), 3.62 (2H, t), 5.83 (2H, s), 7.36 (1H, m), 7.44 (2H, m), 7.65 (1H, s), 7.86 (2H, m). MS (ES^+): 303.0 (42%).

B. Cpd 5b Regioisomers. Isopropylamine (0.18 g, 3 mmol) and a regioisomeric mixture of 4(5)-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carbaldehyde (0.91 g, 3 mmol) were mixed in 1,2-dichloroethane (10 mL), followed by addition of sodium triacetoxyborohydride (0.95 g, 4.5 mmol). The resulting mixture was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resultant mixture was extracted with EtOAc and the combined organic phases were dried over Na_2SO_4. After filtration and concentration, the residue was

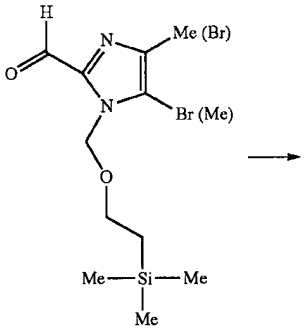
purified by flash column chromatography (eluent: CH_2Cl_2: CH_3OH, 7:3) to give isopropyl-[4(5)-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-ylmethyl]-amine (0.70 g, 68%) as a mixture of regioisomers. ^1H NMR (300 MHz, $CDCl_3$): δ 0.00 (9H, s), 0.94 (2H, t), 1.11 (6H, d), 2.89 (1H, m), 3.56 (2H, t), 3.94 (2H, s), 5.39 (2H, s), 7.25 (2H, m), 7.37 (2H, m), 7.76 (2H, d). MS (ES^+): 346.6 (75%).

Compound 5b may be substituted for Cpd 1d of Example 1 and elaborated to compounds of the present invention with the appropriate reagents, starting materials and purification methods known to those skilled in the art.

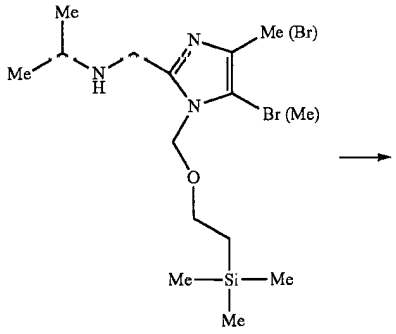
Example 6

2-Amino-3-(4-hydroxy-phenyl)-N-isopropyl-N-(5-methyl-4-phenyl-1H-imidazol-2-ylmethyl)-propionamide Trifluoroacetate (1:2)

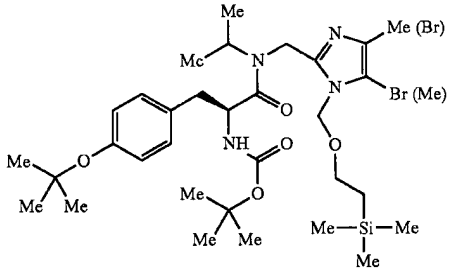
Mixtures of regioisomers



6a

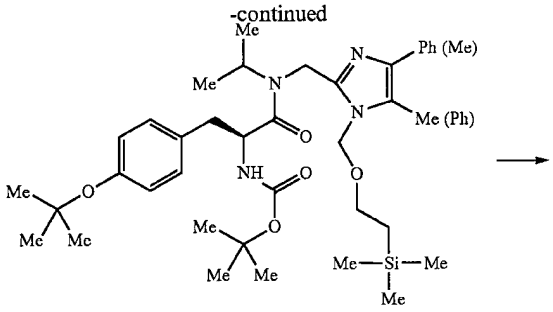


6b

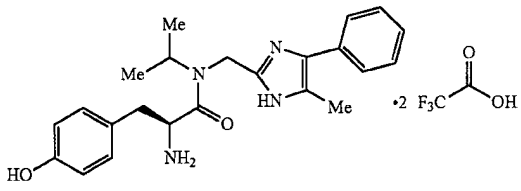


6c

-continued



6d



6e

A. Cpd 6a Regioisomers. Bromine (1.17 mL, 22.76 mmol) was added slowly to an ice cooled regioisomeric mixture of 4(5)-methyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazole-2-carbaldehyde (5.47 g, 22.76 mmol; *JOC*, 1986, 51(10), 1891-4) in $CHCl_3$ (75 mL). The reaction was warmed to rt after 1.5 h, and then was stirred an additional 1 h. The reaction mixture was then extracted with saturated aqueous $NaHCO_3$, and the organic phase was then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 7.46 g of crude material. This material was vacuum distilled (bp 127-135° C.; 1 mm Hg) to yield 3.16 g (43%) of a regioisomeric mixture, Cpd 6a, as a yellow liquid, which was used without further purification. ^1H NMR ($CDCl_3$) δ 0 (s, 9H), 0.9-1.0 (t, 2H), 2.35 (s, 3H), 3.5-3.6 (t, 2H), 5.8 (s, 2H), 9.75 (s, 1H).

B. Cpd 6b Regioisomers. Isopropyl amine (0.30 g, 5 mmol) in 1,2-dichloroethane (2 mL) was added to a 5° C. solution of regioisomers Cpd 6a (0.96 g, 3 mmol) in 1,2-dichloroethane (70 mL). After stirring for 5 min, sodium triacetoxyborohydride (1.80 g, 8.5 mmol) was added neat to the reaction mixture. The mixture was gradually warmed to rt and stirred for 24 h. At this time, an additional portion of sodium triacetoxyborohydride (0.60 g, 2.8 mmol) was added and the reaction was stirred an additional 16 h. The reaction was then cooled to approximately 10° C. and treated while stirring with saturated aqueous $NaHCO_3$. After stirring for 15 min, the layers were separated and the organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give 1.20 g (T.W. 1.09 g) of a regioisomeric mixture, Cpd 6b, as a yellow oil which was used directly without further purification.

C. Cpd 6c Regioisomers. Isobutyl chloroformate (0.43 g, 3.15 mmol) was added neat to a 0° C. solution containing 2-tert-butoxycarbonylamino-3-(4-tert-butoxy-phenyl)-propionic acid (1.21 g, 3.6 mmol; Advanced Chem Tech), N-methylmorpholine (362 μL, 3.3 mmol), and CH_2Cl_2 (60 mL). After stirring 1.5 h, Cpd 6b (1.09 g, 3 mmol) was added to the reaction mixture. The reaction mixture was then warmed to room temperature and stirred for 16 h. The reaction mixture was then adsorbed on silica gel, and flash chromatographed on a silica gel column eluting with 25% ethyl acetate/hexane. The desired fractions were combined and concentrated under reduced pressure to give 715 mg (35%) of regioisomers of

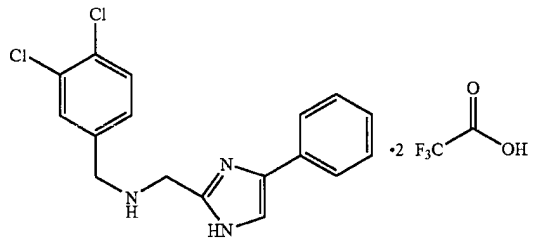
Cpd 6c as a clear oil (TLC: 25% EtOAc/hexane R_f=0.3, homogeneous; HPLC: 100% at 254 and 214 nm, 7.51 min).

D. Cpd 6d Regioisomers. To the regioisomers of Cpd 6c (90 mg, 0.132 mmol) in 1,2-dimethoxyethane (2 mL) was added phenyl boronic acid (32.2 mg, 0.26 mmol) followed by 2M Na_2CO_3(aq) (0.53 mL, 1.06 mmol). The resulting mixture was degassed with N_2 for 5 min and then palladium tetrakis triphenylphosphine (53 mg, 0.046 mmol) was added neat. The reaction vessel was capped and warmed to 80° C. for 14 h with rapid stirring. After cooling to room temperature the mixture was dried over $MgSO_4$, filtered through dicalite, and concentrated under a stream of N_2. The residue was dissolved in a small amount of EtOAc and flash chromatographed on a silica gel column (Eluent: 5%-25% EtOAc/hexane). The desired fractions were concentrated under reduced pressure to yield 55 mg (61%) as regioisomeric mixture of Cpd 6d, which was used without further purification (TLC: 25% EtOAc/hexane R_f=0.3; HPLC: 100% at 254 nm; 88% at 214 nm, 6.50 min).

E. 2-Amino-3-(4-hydroxy-phenyl)-N-isopropyl-N-(5-methyl-4-phenyl-1H-imidazol-2-ylmethyl)-propionamide Trifluoroacetate (1:2). Trifluoroacetic acid (1 mL) was added to the Cpd 6d regioisomers (55 mg, 0.081 mmol) at room temperature. After 6 h, the excess TFA was removed under a stream of N_2. The residue was dissolved in a small amount of acetonitrile and purified by preparative HPLC on a YMC C18 100x20 mm column. The purest fractions were combined and lyophilized to give 37 mg (74%) of the title compound as a white lyophil (TLC: 5:1 $CHCl_3$:MeOH R_f=0.55, homogeneous; HPLC: 100% at 214 nm; HPLC/MS: m/z 393 (MH^+)). ^{1}H NMR (MeOH-d_4) δ 0.85-0.9 (d, 3H), 1.2-1.25 (d, 3H), 2.45 (s, 3H), 3.05-3.1 (t, 2H), 4.0-4.15 (m, 1H), 4.55-4.6 (d, 1H), 4.7-4.85 (m, 2H), 6.65-6.7 (d, 2H), 6.95-7.0 (d, 2H), 7.45-7.6 (m, 5H).

Example 7

(3,4-Dichloro-benzyl)-(4-phenyl-1H-imidazol-2-ylmethyl)-amine Trifluoroacetate (1:2)

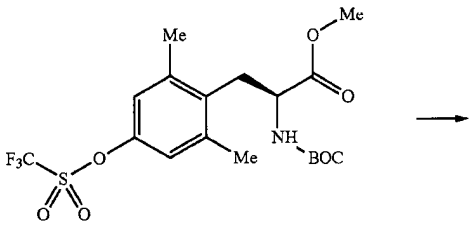


Using the procedure described in Example 5 and substituting 3,4-dichloro-benzylamine for isopropylamine, (3,4-dichloro-benzyl)-[4(5)-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1H-imidazol-2-ylmethyl]-amine was prepared as a pair of regioisomers. A sample (95 mg, 0.21 mmol) of this compound was dissolved in TFA (3 mL) at room temperature. After 2 h the mixture was concentrated under a stream of nitrogen. The residue was purified by reverse phase HPLC, the purest fractions were combined and lyophilized to yield desired product (3,4-dichloro-benzyl)-(4-phenyl-1H-imidazol-2-ylmethyl)-amine as an off white lyophil.

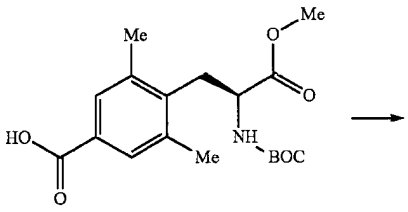
Following the procedure described in Example 1, substituting (3,4-dichloro-benzyl)-(4(5)-phenyl-1H-imidazol-2-ylmethyl)-amine for Cpd 1d, compounds of the present invention may be synthesized with the appropriate reagents, starting materials, and purification methods known to those skilled in the art.

Example 8

(S)-2-tent-Butoxycarbonylamino-3-(2,6-dimethyl-4-trifluoromethanesulfonylphenyl)-propionic acid methyl ester



8a



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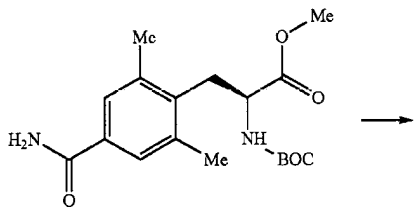

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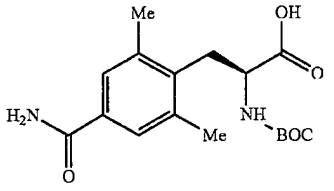


8d

A. (S)-2-tert-Butoxycarbonylamino-3-(2,6-dimethyl-4-trifluoromethanesulfonylphenyl)-propionic acid methyl ester. Into a cool solution of Boc-L-(2,6-diMe)Tyr-OMe (7.0 g, 21.6 mmol; Sources: Chiramer or RSP AminoAcidAnalogues) and N-phenyltrifluoromethanesulfonimide (7.9 g, 22.0 mmol) in dichloromethane (60 mL) was added triethylamine (3.25 mL, 23.3 mmol). The resulting solution was stirred at 0° C. for 1 h and slowly warmed to rt. Upon comple-

tion, the reaction was quenched by addition of water. The separated organic phase was washed with 1N NaOH aqueous solution, water and dried over Na_2SO_4 overnight. After filtration and evaporation, the residue was purified by flash column chromatography (eluent: EtOAc-hexane: 3:7) to give the desired product (9.74 g, 99%) as a clear oil; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.39 (6H, s), 3.06 (2H, d, J=7.7 Hz), 3.64 (3H, s), 4.51-4.59 (1H, m), 5.12 (1H, d, J=8.5 Hz), 6.92 (2H, s); MS (ES+) (relative intensity): 355.8 (100) $(M\text{-}Boc)^+$.

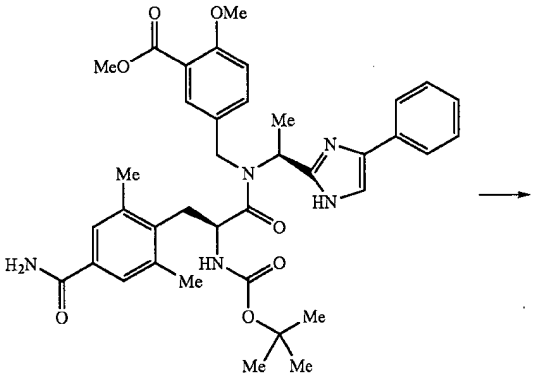
B. (S)-4-(2-tert-Butoxycarbonylamino-2-methoxycarbonylethyl)-3,5-dimethylbenzoic acid. To a suspension of (S)-2-tert-butoxycarbonylamino-3-(2,6-dimethyl-4-trifluoromethanesulfonylphenyl)-propionic acid methyl ester (9.68 g, 21.3 mmol), K_2CO_3 (14.1 g, 0.102 mol), $Pd(OAc)_2$ (0.48 g, 2.13 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (2.56 g, 4.47 mmol) in DMF (48 mL) was bubbled in gaseous CO for 15 min. The mixture was heated to 60° C. for 8 h with a CO balloon. The cool mixture was partitioned between $NaHCO_3$ and EtOAc, and filtered. The aqueous layer was separated, acidified with 10% citric acid aqueous solution, extracted with EtOAc, and finally dried over Na_2SO_4. Filtration and concentration of the filtrate resulted in a residue. The residue was recrystallized from EtOAc-hexanes to afford the desired product (7.05 g, 94%); ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.42 (6H, s), 3.14 (2H, J=7.4 Hz), 3.65 (3H, s), 4.57-4.59 (1H, m), 5.14 (1H, d, J=8.6 Hz), 7.75 (2H, s); MS (ES+) (relative intensity): 251.9 (100) $(M\text{-}Boc)^+$.

C. (S)-2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethylphenyl)propionic acid methyl ester. Into a stirring solution of (S)-4-(2-tert-butoxycarbonylamino-2-methoxycarbonylethyl)-3,5-dimethylbenzoic acid (3.00 g, 8.54 mmol), PyBOP (6.68 g, 12.8 mmol) and HOBt (1.74 g, 12.8 mmol) in DMF (36 mL) was added DIPEA (5.96 mL, 34.2 mmol) and NH_4Cl (0.92 g, 17.1 mmol). The resulting mixture was stirred at rt for 40 min before being partitioned between aqueous NH_4Cl solution and EtOAc. The separated organic phase was washed sequentially with 2N citric acid aqueous solution, saturated aqueous $NaHCO_3$ solution, and brine, then dried over Na_2SO_4 overnight. After filtration and concentration, the residue was purified by flash column chromatography (eluent: EtOAc) to give the product. (3.00 g, 100%); ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.39 (6H, s), 3.11 (2H, J=7.2 Hz), 3.65 (3H, s), 4.53-4.56 (1H, m), 5.12 (1H, d, J=8.7 Hz), 5.65 (1H, br s), 6.09 (1H, br s), 7.46 (2H, s); MS (ES+) (relative intensity): 250.9 (100) $(M\text{-}Boc)^+$.

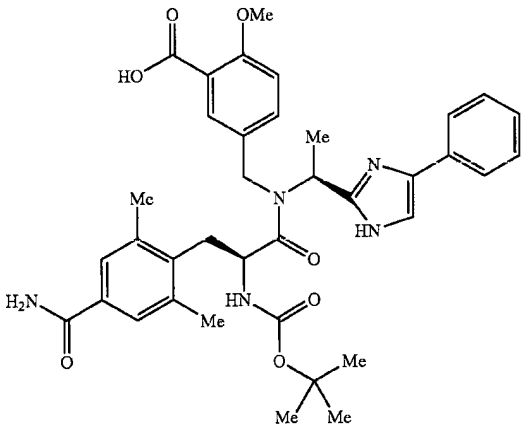
D. (S)-2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethylphenyl)propionic acid. Into an ice-cooled solution of methyl ester from Step C (2.99 g, 8.54 mmol) in THF (50 mL) was added an aqueous LiOH solution (1N, 50 mL) and stirred at 0° C. Upon consumption of the starting materials, the organic solvents were removed and the aqueous phase was neutralized with cooled 1N HCl at 0° C., and extracted with EtOAc, and dried over Na_2SO_4 overnight. Filtration and evaporation to dryness led to the title acid (S)-2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethylphenyl)propionic acid (2.51 g, 87%); ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (9H, s), 2.32 (6H, s), 2.95 (1H, dd, J=8.8, 13.9 Hz), 3.10 (1H, dd, J=6.2, 14.0 Hz), 4.02-4.12 (1H, m), 7.18-7.23 (2H, m), 7.48 (2H, s), 7.80 (1H, s); MS (ES+) (relative intensity): 236.9 (6) $(M\text{-}Boc)^+$.

Example 9

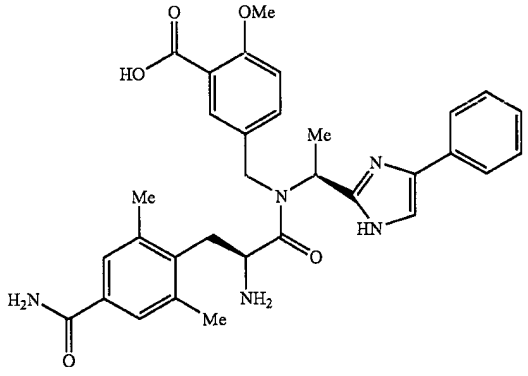
5-({[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid



9a



9b



9c

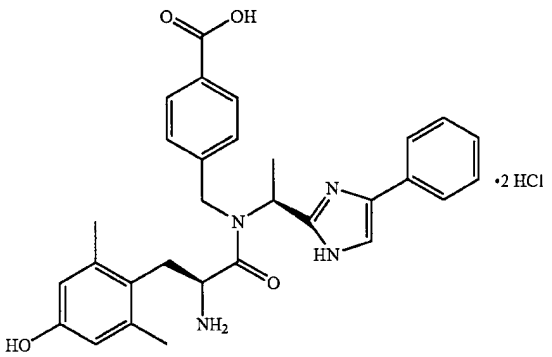
A. 2-Methoxy-5-{[1-(4-phenyl-1H-imidazol-2-yl)-ethylamino]-methyl}-benzoic acid methyl ester. Using the procedures described for Example 3, substituting 5-formyl-2-methoxy-benzoic acid methyl ester (WO 02/22612) for 3,4-dimethoxybenzaldehyde, 2-methoxy-5-{[1-(4-phenyl-1H-imidazol-2-yl)-ethylamino]-methyl}-benzoic acid methyl ester was prepared.

B. 5-({[2-tert-Butoxycarbonyl methyl-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid methyl ester. Using the procedure of Example 1 for the conversion of Cpd 1d to Cpd 1e, substituting 2-methoxy-5-{[1-(4-phenyl-1H-imidazol-2-yl)-ethylamino]-methyl}-benzoic acid methyl ester for Cpd 1d and substituting 2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl-propionic acid of Example 8 for 2-tert-Butoxycarbonylamino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid, Cpd 9a was prepared.

C. 5-({[2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid. 5-({[2-tert-Butoxycarbonylmethyl-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid methyl ester was dissolved in an ice-chilled (0-10° C.), mixed solvent system of THF (10 mL) and MeOH (5 mL). A LiOH.H_2O/water suspension (2.48 M; 3.77 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stirred overnight. The resulting mixture was cooled in an ice bath and the basic solution was neutralized with 2N citric acid until slightly acidic. The mixture was concentrated under reduced pressure to remove the volatile materials, after which time the remaining aqueous phase was extracted with EtOAc (3×26 mL). These combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 2.26 g (146% of theory) of pale yellowish white solid. This crude material was dissolved in a 10% MeOH/CH_2Cl_2 solution and adsorbed onto 30 g of silica. The adsorbed material was divided and chromatographed on an ISCO normal phase column over two runs, using a 40 g Redi-Sep column for both runs. The solvent system was a gradient MeOH/CH_2Cl_2 system as follows: Initial 100% CH_2Cl_2, 98%-92% over 40 min; 90% over 12 min, and then 88% over 13 min. The desired product eluted cleanly between 44-61 min. The desired fractions were combined and concentrated under reduced pressure to yield 1.74 g (113% of theory) of 5-({[2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid, Cpd 9b, as a white solid.

D. 5-({[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid. A portion of Cpd 9b (0.27 g, 0.41 mmol) was dissolved in EtOAc (39 mL)/THF (5 mL), filtered, and subsequently treated with gaseous HCl for 15 min. After completion of the HCl addition, the reaction was slowly warmed to room temperature and a solid precipitate formed. After 5 h the reaction appeared >97% complete by LC (@214 nm; 2.56 min.). The stirring was continued over 3 d, then the solid was collected and rinsed with a small amount of EtOAc. The resulting solid was dried under high vacuum under refluxing toluene for 2.5 h to yield 0.19 g (71%) of desired Cpd 9c as a white solid di-HCl salt.

Example 10



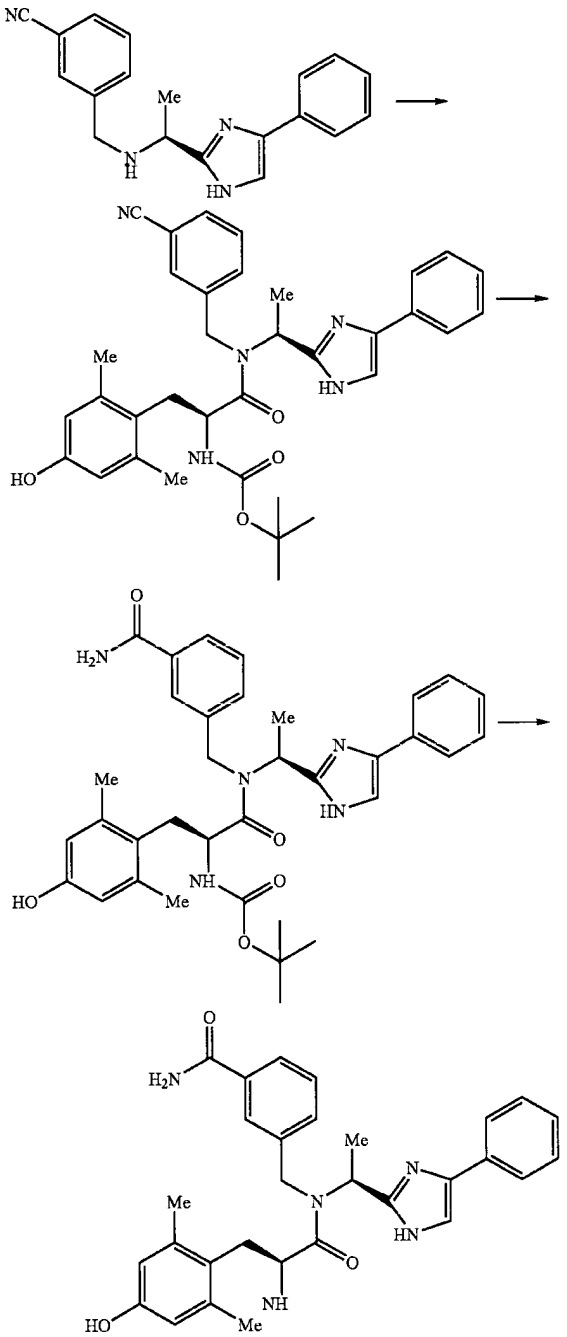
A. 4-{[1-(4-Phenyl-1H-imidazol-2-yl)-ethylamino]-methyl}-benzoic acid methyl ester. Using the procedure described for Example 3, substituting 4-formyl-benzoic acid methyl ester for 3,4-dimethoxybenzaldehyde, 4-{[1-(4-phenyl-1H-imidazol-2-yl)-ethylamino]-methyl}-benzoic acid methyl ester was prepared.

B. 4-({[2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-benzoic acid methyl ester. 4-{[1-(4-phenyl-1H-imidazol-2-yl)ethylamino]-methyl}-benzoic acid methyl ester was substituted for Cpd 1d of Example 1 and elaborated according to the procedure of Example 1 to prepare the product.

C. 4-({[2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-benzoic acid. A solution of 4-({[2-amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-benzoic acid methyl ester (TFA salt), (0.043 g, 0.067 mmol) in 5 mL of THF was cooled in an ice bath. A cold (5-10° C.) 3M aqueous solution of LiOH (5 mL) was added and the reaction mixture was stirred vigorously while cold. Chilled (5-10° C.) 2M aqueous HCl (7.5 mL) was added dropwise to neutralize the mixture was stirred for 5 min, and then partially concentrated in vacuo unheated. The resultant aqueous suspension was extracted seven times with EtOAc. The extracts were dried over Na_2SO_4, filtered, and concentrated to afford 0.030 g of 4-({[2-amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-benzoic acid as a white powder. The material was taken up in EtOH and treated with 1M HCl in Et_2O. The solution was concentrated and the residue was triturated with CH_3CN. A 0.021 g (53%) sample of 4-({[2-amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-benzoic acid was collected as its HCl salt. MS (ES^+) (relative intensity): 513.2 (100) (M+1).

Example 11

3-({[2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-benzamide



A. 3-{[1-(4-phenyl-1H-imidazol-2-yl)-ethylamino]-methyl}-benzonitrile. Using the procedure described for Example 3, substituting 3-formyl-benzonitrile for 3,4-dimethoxybenzaldehyde, the product was prepared.

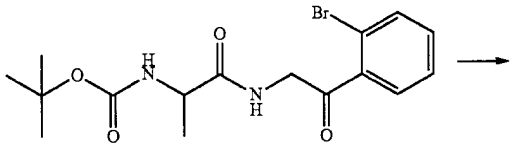
B. [1-{(3-Cyano-benzyl)-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl}-2-(4-hydroxy-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester. 3-{[1-(4-phenyl-1H-imidazol-2-yl)-ethylamino]-methyl}-benzonitrile was substituted for Cpd 1d of Example 1 and elaborated according to the procedure of Example 1 to prepare the product.

C. [1-{(3-Carbamoyl-benzyl)-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl}-2-(4-hydroxy-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester. A solution of [1-{(3-cyano-benzyl)-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl}-2-(4-hydroxy-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester (0.070 g, 0.12 mmol) in 3 mL of EtOH was treated with 1.0 mL of 30% hydrogen peroxide followed immediately by 0.1 mL of a 6M aqueous solution of NaOH. The reaction mixture was stirred vigorously for 18 h and quenched by pouring into chilled (5-10° C.) water. The aqueous solution was extracted five times with Et_2O and the combined extracts were dried over $MgSO_4$, filtered, and concentrated to provide 0.051 g of [1-{(3-carbamoyl-benzyl)-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl}-2-(4-hydroxy-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester as a colorless residue (HPLC: 84% @ 254 nm and 77% @ 214 nm). MS (ES^+) (relative intensity): 612.5 (100) (M+1). This sample was of sufficient quality to use in the next reaction without further purification.

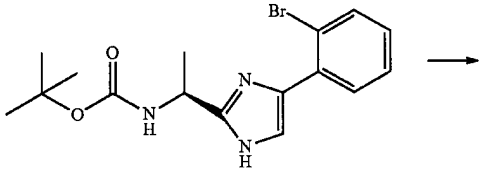
D. 3-({[2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}methyl)-benzamide. [1-{(3-carbamoyl-benzyl)-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-carbamoyl}-2-(4-hydroxy-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester may be BOC-deprotected using the procedure described in Example 1 for the conversion of Cpd 1e to Cpd 1f to provide the title compound.

Example 12

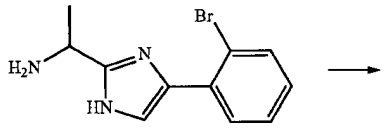
4-{2-Amino-2-[{1-[4-(2-cyano-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-ethyl}-3,5-dimethyl-benzamide



12a



12b



12c

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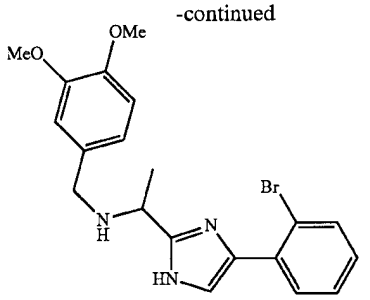
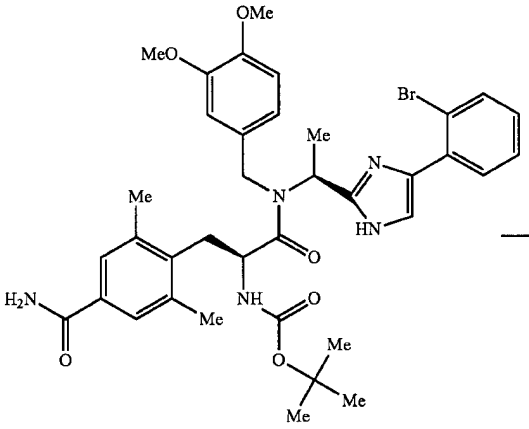
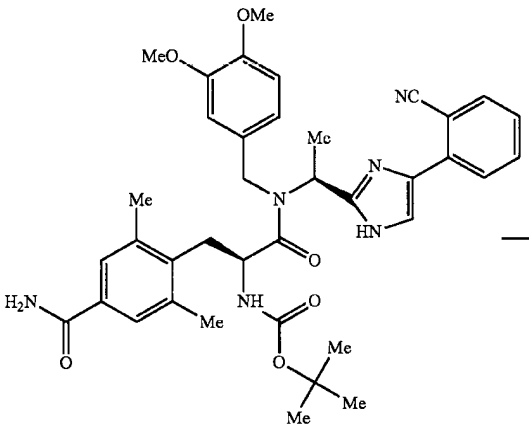


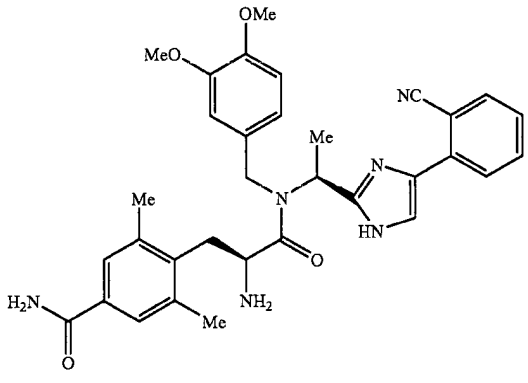
12d



12e



12f



12g

A. {1-[2-(2-Bromo-phenyl)-2-oxo-ethylcarbamoyl]-ethyl}-carbamic acid tert-butyl ester. Compound 2a was prepared according to Example 1 using the appropriate reagents, starting materials and methods known to those skilled in the art.

B. {1-[4-(2-Bromo-phenyl)-1H-imidazol-2-yl]-ethyl}-carbamic acid tert-butyl ester. Following the procedure described in Example 1 for the conversion of Compound 1a to Compound 1b, and using the appropriate reagents and methods known to those skilled in the art, Cpd 12b, was prepared.

C. 1-[4-(4-Bromo-phenyl)-1H-imidazol-2-yl]-ethylamine. Using the procedure described for the conversion of Cpd 1e to 1f, Compound 12c was prepared.

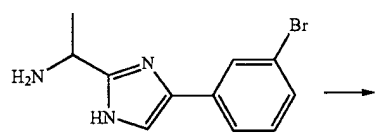
D. [1-[{1-[4-(2-Bromo-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-2-(4-carbamoyl-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester. Using the procedure described in Example 9, Step D, and substituting 1-[4-(4-bromo-phenyl)-1H-imidazol-2-yl]-ethylamine for 1-(4-phenyl-1H-imidazol-2-yl)-ethylamine, the product was prepared.

E. {2-(4-Carbamoyl-2,6-dimethyl-phenyl)-1-[{1-[4-(2-cyano-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-ethyl}-carbamic acid tert-butyl ester. To a solution of [1-[{1-[4-(2-bromo-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-2-(4-carbamoyl-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester (294 mg; 0.4 mmol) in DMF (2 mL) was added $Zn(CN)_2$ (28 mg; 0.24 mmol). The resulting mixture was degassed with Argon for 5 min, then $Pd(PPh_3)_4$ (92 mg; 0.08 mmol) was added neat, and the system was immediately warmed to 100° C. After heating for 6 h, the reaction was cooled to rt and partitioned between EtOAc and water. The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was subjected to reverse phase HPLC (water/acetonitrile/0.1% TFA). The fractions of interest were combined, basified with saturated aqueous $NaHCO_3$ and extracted twice with EtOAc. The EtOAc extracts were combined, dried over Na_2SO_4, filtered, and concentrated to afford 146 mg (54%) of desired {2-(4-carbamoyl-2,6-dimethyl-phenyl)-1-[{1-[4-(2-cyano-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-ethyl}-carbamic acid tert-butyl ester (HPLC: 96% @ 254 nm and 97% @ 214 nm). This sample was of sufficient quality to use in the next reaction without further purification.

F. 4-{2-Amino-2-[{1-[4-(2-cyano-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-ethyl}-3,5-dimethyl-benzamide. {2-(4-carbamoyl-2,6-dimethyl-phenyl)-1-[{1-[4-(2-cyano-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]ethyl}-carbamic acid tert-butyl ester may be BOC-deprotected using the procedure described in Example 1 for the conversion of Cpd 1e to Cpd 1f to give the title compound.

Example 13

3-(2-{1-[[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-(3,4-dimethoxy-benzyl)-amino]-ethyl}-1H-imidazol-4-yl)-benzoic acid



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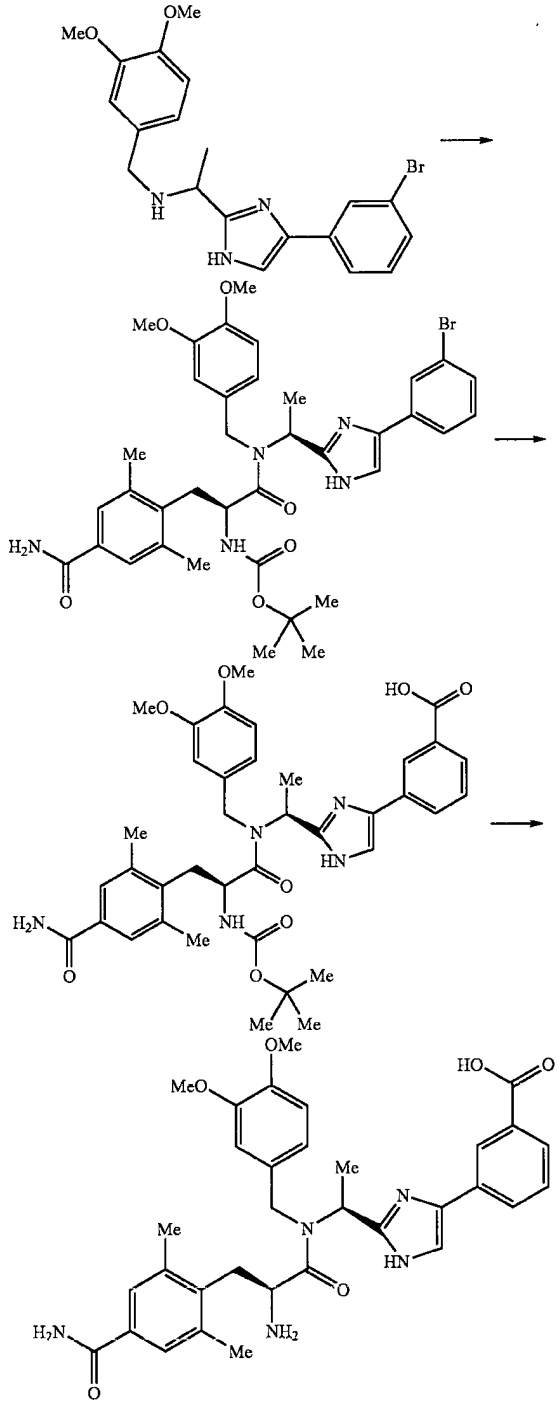


A. 1-[4-(3-Bromo-phenyl)-1H-imidazol-2-yl]-ethylamine. Using the procedure described in Example 12, and the appropriately substituted starting materials and reagents, 1-[4-(3-bromo-phenyl)-1H-imidazol-2-yl]-ethylamine was prepared.

B. {1-[4-(3-Bromo-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-amine-. Using the procedure described in Example 3, and substituting 1-[4-(3-bromo-phenyl)-1H-imidazol-2-yl]-ethylamine for 1-(4-phenyl-1H-imidazol-2-yl)-ethylamine, the product was prepared.

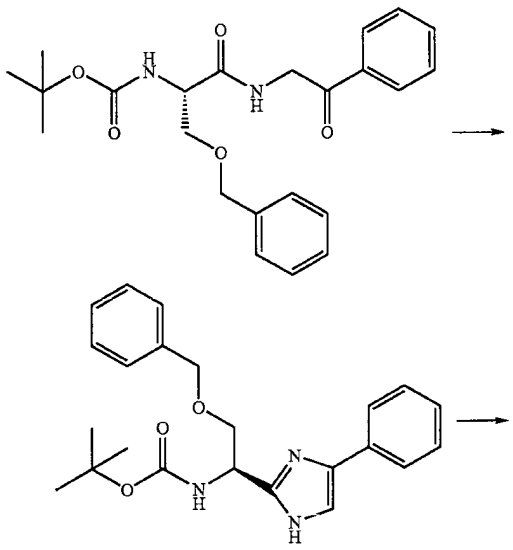
C. [1-[{1-[4-(3-Bromo-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-2-(4-carbamoyl-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester. Using the procedure of Example 1 for the conversion of Cpd 1d to Cpd 1e, substituting {1-[4-(3-Bromo-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-amine for Cpd 1d and substituting 2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl-propionic acid of Example 8 for 2-tert-Butoxycarbonylamino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid, the product was prepared.

D. 3-(2-{1-[[2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-(3,4-dimethoxy-benzyl)-amino]-ethyl}-1H-imidazol-4-yl)-benzoic acid. To a solution of [1-[{1-[4-(3-bromo-phenyl)-1H-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-2-(4-carbamoyl-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester (290 mg; 0.40 mmol) in DMF (5 mL) was added K_2CO_3 (262 mg; 1.9 mmol) and the resulting mixture was degassed with Argon for 5 min. At this time, $Pd(OAc)_2$ (8.9 mg; 0.04 mmol) and 1,1-bis(diphenylphosphino) ferrocene (46 mg; 0.083 mmol) were added. Carbon monoxide was then bubbled through the resulting mixture for 10 min at rt, the reaction was capped, and warmed to 100° C. for 6 h. After cooling to rt the mixture was partitioned between EtOAc and water, filtered through Celite, and then separated. The aqueous phase was then washed with a second portion of EtOAc. The aqueous phase was then acidified to pH 5 with 2N citric acid and the resulting aqueous solution extracted with EtOAc (4×). These latter EtOAc extracts were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product (HPLC: 87% at 254 nm).

E. 3-(2-{1-[[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-(3,4-dimethoxy-benzyl)-amino]-ethyl}-1H-imidazol-4-yl)-benzoic acid. 3-(2-{1-[[2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-(3,4-dimethoxy-benzyl)-amino]-ethyl}-1H-imidazol-4-yl)-benzoic acid may be BOC-deprotected using the procedure described in Example 1 for the conversion of Cpd 1e to Cpd 1f to give the title compound.

Example 14

4-(2-Amino-2-{[2-hydroxy-1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-isopropyl-carbamoyl}-ethyl)-3,5-dimethyl-benzamide



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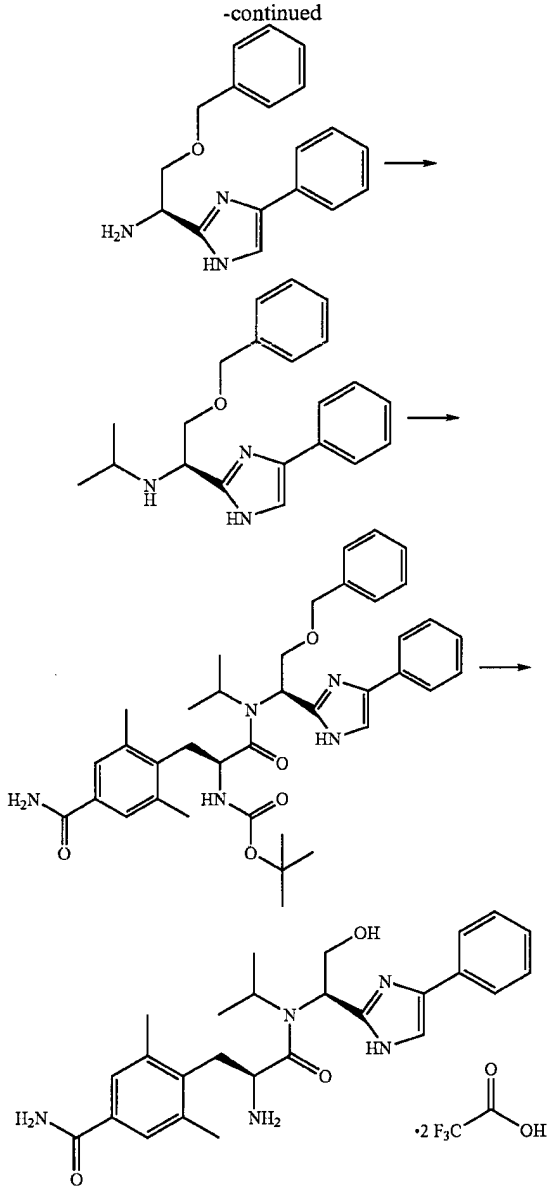


A. [2-Benzyloxy-1-(2-oxo-2-phenyl-ethylcarbamoyl-ethyl]carbamic acid tert butyl ester. The product was prepared using the procedure described in Example 1 and substituting N-α-BOC-L-serine benzyl ester for N-α-CBZ-L-alanine.

B. [2-Benzyloxy-1-(4-phenyl-1H-imidazol-2-yl-ethyl] carbamic acid tert butyl ester. By the procedure described in Example 1 for the conversion of Cpd 1a to Cpd 1b, [2-benzyloxy-1-(2-oxo-2-phenyl-ethylcarbamoyl-ethyl]-carbamic acid tert butyl ester was converted to the product.

C. [2-Benzyloxy-1-(4-phenyl-1H-imidazol-2-yl-ethylamine. [2-benzyloxy-1-(4-phenyl-1H-imidazol-2-yl-ethyl]-carbamic acid tert butyl ester may be BOC-deprotected using the procedure described in Example 1 for the conversion of Cpd 1e to Cpd 1f to give the product.

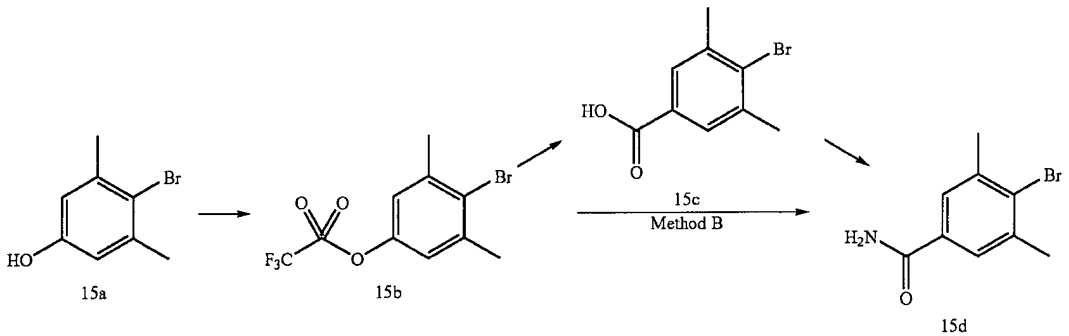
D. [2-Benzyloxy-1-(4-phenyl-1H-imidazol-2-yl-ethyl]-isopropyl-amine. By the procedure described in Example 1 for the conversion of Cpd 1c to Cpd 1d, [2-benzyloxy-1-(4-phenyl-1H-imidazol-2-yl-ethylamine was converted to the product.

E. [1-{[2-Benzyloxy-1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-isopropyl-carbamoyl}-2-(4-carbamoyl-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester. Using the procedure of Example 1 for the conversion of Cpd 1d to Cpd 1e, substituting [2-benzyloxy-1-(4-phenyl-1H-imidazol-2-yl-ethyl]-isopropyl-amine for Cpd 1d and substituting 2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl-propionic acid of Example 8 for 2-tert-butoxycarbonylamino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionic acid, the product was prepared.

F. 4-(2-Amino-2-{[2-hydroxy-1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-isopropyl-carbamoyl}-ethyl)-3,5-dimethyl-benzamide (TFA salt). A solution of [1{[2-benzyloxy-1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-isopropyl-carbamoyl}-2-(4-carbamoyl-2,6-dimethyl-phenyl)-ethyl]-carbamic acid tert-butyl ester, (0.287 g, 0.439 mmol), in chloroform (10 mL) was cooled in an ice bath and treated with 0.62 mL (4.4 mmol) of iodotrimethylsilane. The reaction, which immediately clouded, was warmed slowly to room temperature while stirring. After 16 h, the reaction was cooled in an ice bath to 5-10° C. and treated with 100 mL of MeOH. The quenched mixture was stirred at 5-10° C. for 30 min, removed from the ice bath and stirred for an additional 30 min, and concentrated in vacuo to obtain 0.488 g of orange residue that was subjected to reverse phase HPLC (water/acetonitrile/0.1% TFA). The fractions of interest were combined and the sample was lyophilized to afford 0.150 g (59%) of 4-(2-amino-2-{[2-hydroxy-1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-isopropyl-carbamoyl}-ethyl)-3,5-dimethyl-benzamide (TFA salt) as a white powder (HPLC: 99% @ 254 nm and 100% @ 214 nm). MS (ES+) (relative intensity): 464.1 (100) (M+1).

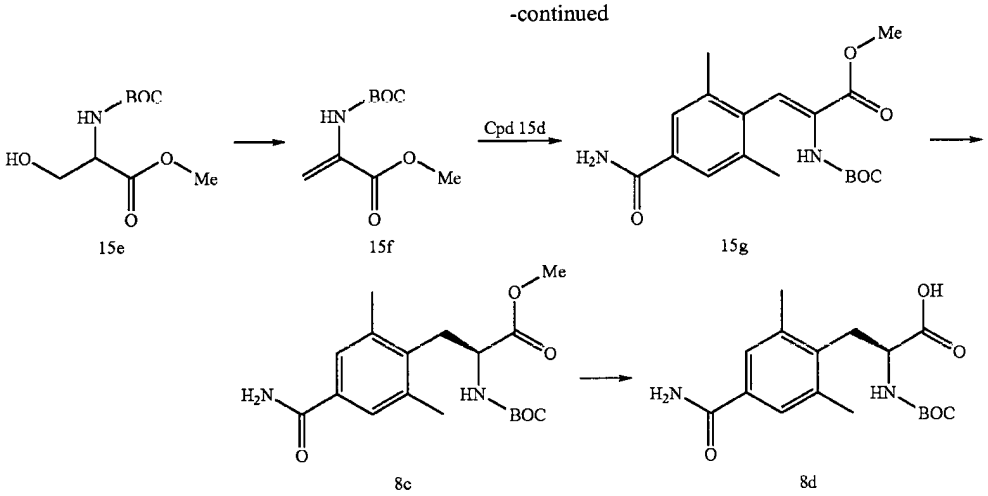
Example 15

(S)-2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2, 6-dimethyl-phenyl)-propionic acid



15a 15b 15d

-continued



A. Trifluoromethanesulfonic acid 4-bromo-3,5-dimethylphenyl ester. To a cooled (0° C.) solution of 4-bromo-3,5-dimethylphenol (3.05 g, 15.2 mmol) in pyridine (8 mL) was added trifluoromethanesulfonic anhydride (5.0 g, 17.7 mmol) dropwise. After completion of addition, the resulting mixture was stirred at 0° C. for 15 min, and then at rt overnight. The reaction was quenched by addition of water, and then extracted with EtOAc. The organic extracts were washed sequentially with water, 2N HCl (2×), brine, and then dried over $MgSO_4$. Filtration and evaporation to dryness afforded Compound 15b (5.30 g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (6H, s), 7.00 (2H, s).

B. 4-Bromo-3,5-dimethylbenzoic acid. To a solution of Compound 15b (6.57 g, 19.7 mmol) in DMF (65 mL) were added K_2CO_3 (13.1 g, 94.7 mmol), $Pd(OAc)_2$ (0.44 g, 1.97 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (2.29 g, 4.14 mmol). The resulting mixture was bubbled in gaseous CO for 10 min and was heated to 60° C. for 7.5 h with a $CO_{(g)}$ balloon. The cooled mixture was partitioned between aqueous $NaHCO_3$ and EtOAc, and filtered. The aqueous phase was separated, acidified with aqueous 6N HCl, extracted with EtOAc, and finally dried over Na_2SO_4. Filtration and concentration of the filtrate resulted in the crude Compound 15c as a brown residue, which was used in the next step without further purification.

C. 4-Bromo-3,5-dimethyl-benzamide. A suspension of Compound 15c in DCM (40 mL) was added $SOCl_2$ (3.1 mL, 42 mmol) and the mixture was heated at reflux for 2 h. Upon removal of the solvent by evaporation, the residue was dissolved in DCM (40 mL) and ammonium hydroxide (28% NH_3 in water, 2.8 mL) was added. The mixture was heated at 50° C. for 2 h and concentrated. The residue was diluted with H_2O, extracted with EtOAc, and the organic portion was dried over Na_2SO_4. After filtration and evaporation, the residue was purified by flash column chromatography (eluent: EtOAc) to give the Compound 15d (2.90 g, 65% for 2 steps) as an off-white solid. ^{1}H NMR (300 MHz, CD_3CN): δ 2.45 (6H, s), 5.94 (1H, br s), 6.71 (1H, br s), 7.57 (2H, s); MS (ES^+) (relative intensity): 228.0 (100%) (M+1).

Method B: A mixture of Compound 15b (3.33 g, 10 mmol), $PdCl_2$ (0.053 g, 0.3 mmol), hexamethyldisilazane (HMDS, 8.4 mL, 40 mmol), and dppp (0.12 g, 0.3 mmol) was bubbled with a gaseous CO for 5 min and then stirred in a CO balloon at 80° C. for 4 h. To the reaction mixture was added MeOH (5 mL). The mixture was stirred for 10 min, diluted with $2NH_2SO_4$ (200 mL), and then extracted with EtOAc. The EtOAc extract was washed with saturated aqueous $NaHCO_3$, brine, and then dried over Na_2SO_4. Filtration and evaporation of the resultant filtrate gave a residue, which was purified by flash column chromatography (eluent: EtOAc) to give Compound 15d (1.60 g, 70%) as a white solid.

D. 2-tert-Butoxycarbonylaminoacrylic acid methyl ester. To a suspension of N-Boc-serine methyl ester (Cpd 15e, 2.19 g, 10 mmol) and EDC (2.01 g, 10.5 mmol) in DCM (70 mL) was added CuCl (1.04 g, 10.5 mmol). The reaction mixture was stirred at rt for 72 h. Upon removal of the solvent, the residue was diluted with EtOAc, washed sequentially with water and brine and then dried over $MgSO_4$. The crude product was purified by flash column chromatography (eluent: EtOAc:hexane~1:4) to give Compound 15e (1.90 g, 94%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (9H, s), 3.83 (3H, s), 5.73 (1H, d, J=1.5 Hz), 6.16 (1H, s), 7.02 (1H, s).

E. (Z)-2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)acrylic acid methyl ester. A flask charged with Compound 15d (0.46 g, 2.0 mmol), Compound 15f (0.80 g, 4.0 mmol), tri-o-tolylphosphine (0.098 g, 0.32 mmol), DMF (8 mL) was purged with $N_{2\ (g)}$ 3 times. After the addition of tris(dibenzylideneacetone)dipalladium (0) (0.074 g, 0.08 mmol) and TEA (0.31 mL, 2.2 mol), the reaction mixture was heated at 110° C. for 24 h. At that time, the reaction was quenched by addition of water, and then extracted with EtOAc. The organic phase was washed with 1N HCl, saturated aqueous $NaHCO_3$, brine, and dried over $MgSO_4$. The mixture was concentrated to a residue, which was purified by flash column chromatography (eluent: EtOAc:hexane~1:1 to EtOAc only) to give Compound 15 g (0.40 g, 57%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ 1.36 (9H, s), 2.26 (6H, s), 3.83 (3H, s), 7.10 (1H, s), 7.56 (2H, s); ^{13}C NMR (75 MHz, DMSO-d_6): δ 17.6, 25.7, 50.2, 78.7, 124.9, 126.4, 128.3, 131.2, 135.2, 135.5, 152.8, 164.3, 169.6; MS (ES^+) (relative intensity): 349.1 (38%) (M+1).

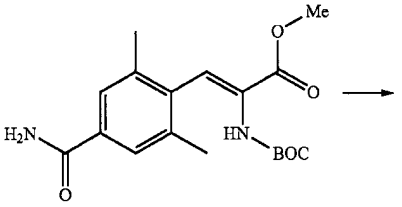
F. (S)-2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid methyl ester. Into a reactor charged with a solution of Compound 15 g (0.56 g, 1.6 mmol) in degassed MeOH (80 mL) was added [Rh(cod)(R,R-DIPAMP)]$^+BF_4^-$ under a stream of argon. The reactor was sealed and flushed with H_2, stirred at 60° C. under 1000 psi of H_2 for 14 d. The crude product was purified by flash column chromatography (eluent: EtOAc:hexane~1:1) to afford Compound 8c (0.54 g, 96%) as a white solid. ee: >99%; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.39 (6H, s), 3.11 (2H, J=7.2 Hz), 3.65 (3H, s), 4.53-4.56 (1H, m), 5.12 (1H, d, J=8.7 Hz), 5.65 (1H, br s), 6.09 (1H, br s), 7.46 (2H, s); MS (ES^+) (relative intensity): 250.9 (100) $(M\text{-}Boc)^+$.

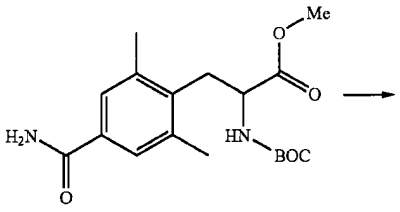
G. (S)-2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid. Into an ice-cooled solution of Compound 8c (0.22 g, 0.63 mmol) in THF (3.5 mL) was added an aqueous LiOH solution (1 N, 3.5 mL) and stirred at 0° C. Upon completion of the reaction, the reaction was concentrated and the aqueous phase was neutralized with cooled aqueous 1 N HCl at 0° C., and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 overnight. Filtration and evaporation of the filtrate to dryness led to Compound 8d (0.20 g, 94%) as a white solid. ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (9H, s), 2.32 (6H, s), 2.95 (1H, dd, J=8.8, 13.9 Hz), 3.10 (1H, dd, J=6.2, 14.0 Hz), 4.02-4.12 (1H, m), 7.18-7.23 (2H, m), 7.48 (2H, s), 7.80 (1H, s); MS (ES^+) (relative intensity): 236.9 (6) $(M\text{-}Boc)^+$.

Example 16

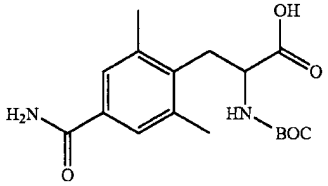
Racemic 2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionic acid



Cpd 15g



16a



16b

A. Racemic 2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid methyl ester. To a reactor charged with a solution of Compound 15 g (0.68 g, 1.95 mmol) in MeOH (80 mL) was added 10% Pd—C (0.5 g). The reactor was connected to a hydrogenator and shaken under 51 psi of H_2 overnight. The mixture was filtered through a pad of Celite and the filtrate was concentrated to dryness to give Compound 16a (0.676 g, 99%) as a white solid. The ^1H NMR spectrum was identical to that of (S)-2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid methyl ester, Compound 8c.

B. Racemic 2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid. Using the procedure described for Example 15, for the preparation of (S)-2-tert-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid, racemic 2-tert-butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)propionic acid, Compound 16b, was prepared.

Using the procedures of the Examples above and the appropriate reagents, starting materials and purification methods known to those skilled in the art, other compounds of the present invention may be prepared including but not limited to:

TABLE VI

Mass Spectral Data for Selected Compounds

Cpd	Theoretical MW	Measured MW (MH^+)
1	538	539
2	520	521
3	573	574
4	541	542
5	527	528
6	555	556
7	569	570
8	593	594
9	553	554
10	603	604
11	589	590
12	587.2	588.3
13	589.3	590.2
14	569.3	570.2
15	500.2	499.2
16	475.3	476.1
17	583.28	584.5
18	569.26	570.2
19	633.2	634.0
20	599.3	600.2
21	634.3	635.2
22	634.3	635.2
23	598.3	599.2
24	580.3	581.1
25	471.26	472.4
26	633.2	634.0
27	580.3	581.1
28	598.3	599.2
29	599.3	600.0
30	680.3	681.2
31	512.2	513
32	498.3	499.1
33	498.3	499.1
34	528.3	529.2
35	514.3	515.1
36	462.26	463.4
37	482.23	483.4
38	446.27	447.5
39	450.26	451.5
40	530.3	531.2
41	445.3	446.1
42	563.3	564.2
43	504.23	505.3
44	504.23	505.3
45	513.24	514.3
46	492.27	493.2
47	479.25	480.1
48	512.2	513.2
49	540.2	541
50	539.25	540.2
51	553.3	554.1
52	526.3	527.1
53	609.3	610.2
54	458.2	459
55	458.2	459
56	474.3	475.2
57	469.25	470.1
58	543.2	544.3
59	513.3	514.2
60	445.3	446.2
61	456.2	457.1

TABLE VI-continued

Mass Spectral Data for Selected Compounds

Cpd	Theoretical MW	Measured MW (MH^+)
62	498.2	499.1
63	436.3	437.1
64	601.3	602.2
65	422.1	423.1
66	463.3	464.5
67	491.3	492.1
68	436.3	437.1
69	463.3	464.1
70	454.2	455.0
71	456.2	457.0
72	498.2	499.1
73	463.3	464.2
74	577.3	578.6
75	555.3	555.8
76	513.3	514.2
77	525.3	526.3
78	497.3	498.3
79	525.3	526.2
80	512.2	513.2
81	484.2	485.4
82	438.24	439.2
83	486.24	487.5
84	438.24	439.0
85	463.3	464.2
86	433.2	434.2
87	522.2	523
88	526.3	527.4
89	526.3	527.4
90	511.3	512.4
91	493.2	494.4
92	469.2	470.2
93	469.2	470.4
94	495.3	496.2
95	495.3	496.2
96	498.3	499.2
97	536.2	537.2
98	560.3	561.2
99	518.3	519.2
100	518.3	519.2
101	546.2	547.2
102	528.3	529.2
103	536.2	537.2
104	510.3	511.2
105	544.3	545.3
106	496.3	497.2
107	481.3	482.3
108	523.3	524.8
109	509.3	510.4
110	509.3	510.3
111	509.3	510
112	509.3	510
113	495.3	496.4
114	495.3	496.1
115	496.28	497.4
115	496.28	497.4
116	438.24	439.4
117	438.24	439.4
118	436.2	437.3
119	394.2	395.2
120	525.3	526.2
121	539.3	540.3
122	521.3	522.3
123	464	465
124	421	422
125	450.26	451.5
126	456.23	457.3
127	487.3	488.5
128	487.3	488.6
129	422.2	423.3
130	450	451
131	422.2	423.3
132	394.2	395.2
133	464.2	465.3
134	496.3	497.4
135	450.26	451.37

TABLE VI-continued

Mass Spectral Data for Selected Compounds

Cpd	Theoretical MW	Measured MW (MH^+)
136	495.3	496.4
137	447.3	448.4
138	526.3	527.4
139	653.4	654.5
140	462.3	463.4
141	488.17	489.16
142	450.26	451.40
143	447.3	448.4
144	419.2	420.3
145	496.28	497.32
146	426.21	427.39
147	454.21	455.22
148	477.3	478
149	488.2	489
150	470.3	471
151	488.2	489
152	398.2	399
153	393	394
154	392	393
155	454.21	455.21
156	470.27	471.36
157	477.2	478.4
158	468.2	469.4
159	496.3	497.4
160	429.2	430.4
161	420.2	421.4
162	448.3	449.4
163	438.24	439.1
164	556.23	557.1
165	434.27	435.1
166	420.25	421.1
167	449.3	450.2
168	433.3	434.2
169	415.2	416.2
170	434.3	435.3
171	392.2	393.3
172	497.2	498.3
173	479.2	480.3
174	434.3	435.3
175	484.2	485.2
176	420.2	421.4
177	454.2	455.3
178	433.3	434.1
179	489.3	490.1
180	489.3	489.9
181	447.3	448.1
182	447.3	448.3
183	433.3	434.2
184	433.3	434.2
185	405.2	406.2
186	387.2	388.2
187	406.2	407.2
188	378.2	379.2
189	427.2	428
190	446.3	447.4
191	418.2	419.4
192	418.2	419.3
193	390.2	391.3
194	406.2	407.5
195	378.2	379.3
196	419.2	420.4
197	433.3	434.1
198	350.2	351.1
199	378.2	379.2
202	391.2	392
203	391.2	391.9
204	378.2	379
205	406.2	407
206	392.2	393.3
207	392.2	393.2
208	378.2	379.3
209	378.2	379.2
210	364.2	365.2
211	364.2	365.2
212	350.2	351.2

TABLE VI-continued

Mass Spectral Data for Selected Compounds

Cpd	Theoretical MW	Measured MW (MH^+)
213	350.2	351.1
214	378.2	379.1
215	378.2	379.1
216	406.2	407.2
217	406.2	407.1
218	468.3	469.4
219	440.2	441.3
220	468.3	469.4
221	440.2	441.2
222	392.2	393.2
223	420.3	421.2
224	420.3	421.1
225	392.2	393.2
226	539	540
227	539	540
228	587	588
229	633	634
230	599.3	599.8
231	512.2	513.2
239	617.2	618.2
242	563.3	564.2
246	519.3	520.0
247	548.3	549.2
248	552.2	553.2
249	536.2	537.0
250	526.3	527.2
251	512.3	513.2
252	554.3	555.3
253	540.2	541.2
254	540.2	541.2
255	554.3	555.3
256	529.2	530.2
257	543.2	543.9
260	542.2	543.2
261	514.2	515.1
262	528.2	529.1
266	512.2	513.2
267	535.2	536.0
268	556.3	557.2
269	525.2	526.0
270	511.2	512.2
271	539.2	540.2
272	525.2	526.0
273	541.2	542.4
274	618.3	619.2
275	589.2	590.2
276	559.2	560.2
277	559.2	560.2
278	617.2	618.2
279	528.2	528.9
280	583.3	584.4
281	555.2	556.2
282	569.3	570.2
283	541.2	542.2
284	555.2	556.3
285	541.2	542.4
286	516.2	517.0
287	502.2	503.1
288	648.6	648.0
289	695.2	695.7
290	648.6	648.0
291	648.6	648.0
292	526.3	527.4
293	562.2	563.2
294	562.2	563.2
295	568.3	569.3
296	638.3	638.8
297	513.2	513.7
298	583.3	583.8
299	612.3	613.3
300	608.3	609.3
301	644.3	644.7
303	515.2	515.8
304	501.2	502.2
305	617.3	617.8

TABLE VI-continued

Mass Spectral Data for Selected Compounds

Cpd	Theoretical MW	Measured MW (MH^+)
306	661.3	661.8
307	566.3	566.8
308	661.3	661.8
309	649.3	650.0
310	641.3	642.3
311	554.3	555.3
312	554.3	555.3
313	554.3	555.3
314	554.3	555.3
315	627.3	628.3
316	540.2	541.3
317	540.2	541.3
318	589.2	590.2

Biological Examples

Opioid receptor binding affinity of the compounds of the present invention was determined according to the following procedures and the indicated results were obtained.

Example 1

Rat Brain Delta Opioid Receptor Binding Assay

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, N.Y.) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon® glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 80 mL Tris and centrifuged at 39,000×g for 10 min. The pellet is resuspended in the same volume of Tris buffer containing 5 mM $MgCl_2$ with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the delta opioid binding assays. Following incubation with the delta selective peptide ligand ~4 nM [^{3}H]DPDPE at 25° C. for 2.5 h in a 96-well plate with total volume of 1 mL, the plate contents are filtered through Wallac filtermat B sheets on a Tomtec 96-well harvester. The filters are rinsed three times with 2 mL of 10 mM HEPES (pH 7.4), and dried in a microwave oven 2 min twice. To each sample area 2×504 of Betaplate Scint scintillation fluid (LKB) is added and analyzed on a LKB (Wallac) 1205 BetaPlate liquid scintillation counter.

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested). % inhibition is calculated as: [(total dpm-test compound dpm)/(total dpm-nonspecific dpm)]*100. Kd and K_i values were calculated using GraphPad PRISM data analysis program. The biological activity of the compounds of the present invention is shown in Table VII.

Example 1a

Rat Brain Delta Opioid Receptor Binding Assay

Version 1a

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, N.Y.) were killed by cervical dislocation, and their

brains removed and placed immediately in ice-cold Tris HCl buffer (50 mM, pH 7.4). The forebrains were separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains were homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate was diluted to a concentration of 1 g of forebrain tissue per 80 mL Tris and centrifuged at 39,000×g for 10 min. The pellet was resuspended in the same volume of Tris buffer containing 5 mM $MgCl_2$ with several brief pulses from a Polytron homogenizer. This particulate preparation was used for the delta opioid binding assay. Following incubation with 0.1 nM of the delta selective ligand [^{3}H]naltrindole at 25° C. for 2.5 h in a 96-well plate with total 1 mL, the plate contents were filtered through Wallac filtermat B sheets on a Tomtec 96-well harvester. The filters were rinsed three times with 2 mL of 10 mM HEPES (pH 7.4), and dried in a microwave oven. To each sample area, Betaplate Scint scintillation fluid (LKB) was added and the resulting radioactivity quantified on a LKB (Wallac) 1205 BetaPlate liquid scintillation counter. Kd and Ki values were calculated using the GraphPad PRISM data analysis program. The biological activity of the compounds of the present invention is shown in Table VII.

Example 2

Rat Brain Mu Opioid Receptor Binding Assay

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, N.Y.) are killed by cervical dislocation, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains are separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains are homogenized in Tris buffer in a Teflon® glass homogenizer. The homogenate is diluted to a concentration of 1 g of forebrain tissue per 80 mL Tris and centrifuged at 39,000×g for 10 min. The pellet is resuspended in the same volume of Tris buffer containing 5 mM $MgCl_2$ with several brief pulses from a Polytron homogenizer. This particulate preparation is used for the mu-opioid binding assays. Following incubation with the mu selective peptide ligand .about.0.8 nM [^{3}H] DAMGO at 25° C. for 2.5 h in a 96-well plate with total 1 mL, the plate contents are filtered through Wallac filtermat B sheets on a Tomtec 96-well harvester. The filters are rinsed three times with 2 mL of 10 mM HEPES (pH7.4), and dried in a microwave oven 2 min twice. To each sample area 2×50 μL of Betaplate Scint scintillation fluid (LKB) is added and analyzed on a LKB (Wallac) 1205 BetaPlate liquid scintillation counter.

The data are used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound is evaluated) or a K_i value (when a range of concentrations is tested). % inhibition is calculated as: [(total dpm-test compound dpm)/(total dpm-nonspecific dpm)]*100. Kd and Ki values were calculated using GraphPad PRISM data analysis program. The biological activity of the compounds of the present invention is shown in Table VII.

Example 2a

Rat Brain Mu Opioid Receptor Binding Assay

Version 2a

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, N.Y.) were killed by cervical dislocation, and their brains removed and placed immediately in ice-cold Tris HCl buffer (50 mM, pH 7.4). The forebrains were separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains were homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate was diluted to a concentration of 1 g of forebrain tissue per 80 mL Tris and centrifuged at 39,000×g for 10 min. The pellet was resuspended in the same volume of Tris buffer containing 5 mM $MgCl_2$ with several brief pulses from a Polytron homogenizer. This particulate preparation was used for the mu opioid binding assay. Following incubation with 0.8 nM of the mu selective ligand [^{3}H]DAMGO at 25° C. for 2.5 h in a 96-well plate with total 1 mL, the plate contents were filtered through Wallac filtermat B sheets on a Tomtec 96-well harvester. The filters were rinsed three times with 2 mL of 10 mM HEPES (pH 7.4), and dried in a microwave oven. To each sample area, Betaplate Scint scintillation fluid (LKB) was added and the resulting radioactivity quantified on a LKB (Wallac) 1205 BetaPlate liquid scintillation counter. Kd and Ki values were calculated using the GraphPad PRISM data analysis program.

TABLE VII

Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
1	13.2		1.1
2			
3			
4	11, 17		2.41
5	630, 183		1.19
6	1.7		
7			
8	0.43, 0.15		0.51
9	0.11		0.16
10			
11	0.54		0.23
12	0.08		
13			
14	0.36		
15			
16			
17	60		0.22
18	0.38-14.4		0.75, 1.1
19			
20			
21			
22			
23			
24			
25			
26			
27			
28			
29	28		25
30			
31			
32			
33			
34			
35			
36			
37			
38			
39			
40			
41			
42			
43			
44			
45			
46			

TABLE VII-continued

Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
47			
48		0.24	0.14
49			
50	0.58		1.68
51			
52			
53			
54			
55			
56			
57			
58			
59			
60			
61			
62			
63			
64			
65			
66			
67			
68			
69			
70			
71			
72			
73			
74			
75	0.66		0.51
76			
77			
78			
79			
80			
81			
82			
83			
84			
85			
86			
87			
88			
89			
90			
91			
92			
93			
94			
95			
96			
97			
98			
99			
100			
101			
102			
103			
104			
105			
106			
107			
108			
109			
110			
111			
112			
113			
114	12		0.26
115			
116			
117			
118			
119			
120			
121			
122			

TABLE VII-continued

Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
123			
124			
125			
126			
127			
128			
129			
130			
131			
132			
133			
134			
135			
136			
137			
138			
139			
140			
141			
142			
143			
144			
145			
146			
147			
149			
150			
151			
152			
153			
154			
155			
156			
157			
158			
159			
160			
161			
162			
163	4.51		0.03
164	120		0.38
165	23.6		0.07
166	5.58, 12.03		0.03, 0.07
167	10000		3.15
168	8867		5322
169	10000		853
170	32.6		0.48
171	10000		141
172	10000		150
173	5069		45.7
174			
175	166		3.60
176	10000		156
177	255		13.4
178	104		0.6
179	10000		7116
180	5221		1209
181	341		1.3
182	1859		7
183	604		4
184	10000		19.5
185	182		6716
186	515		5314
187	5198		121
188	541		307
189	360		277
190	13.8		2.61
191	727.3		189
192	7.64		0.09
193	182.1		21.1
194	14.8		0.06
195	306.2		9.29
196			
197	4.27		0.9
198	5178		152

TABLE VII-continued

Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
199	26.3		0.3
202	31.5		5.9
203	49.3		29.1
204			
205	4.44		0.14
206	5.8		0.2
207	5.3, 5.37, 14.7		0.05, 0.08, 0.1
208	33		1.3
209	708		17
210	1862		420.3
211	180		5.9
212	1278		103
213	5658		1263
214	308		44
215	126		0.43
216	1.14		0.04
217	5.4		1.08
218	1.45		0.03
219	87.83		0.87
220	6921		157.2
221	9.58		0.36
222	394		91.2
223	2.6		0.87
224	1.41		0.03
225	112		0.73
226	48		
227	0.08, 0.46		0.96
228	27.8		0.35
229			
230	10		5
231	1070		6.19
239	0.1		0.44
242	0.18		0.59
246	0.035		0.15
247	0.4		0.61
248	0.44		0.11
249	0.18		0.12
250	0.21		0.06
249	0.18		0.12
250	0.21		0.06
251	0.26		0.08
249	0.18		0.12
250	0.21		0.06
251	0.26		0.08
256	3.82		7.08
257		14.0	1.22
260	0.13		0.24
261	8.01		0.79
262	17.5		1.1
266			
267	0.46		1.53
268			
269	0.61	6.24	0.37
270	1.03	4.47	1.37
271	12.2		0.27
272	15.6		1.1
273	1140		754
274			
275	0.47		0.69
276	115		47
277	0.14		0.44
278	49		12
279	5.2		0.137
280	32		3
281	721		399
282	907		185
283	6735		3572
284	1526		1033
285	2897		1868
286	0.11		0.05
287	0.14		0.13
288	0.17		0.43
288	0.17		0.43
289	0.1, 3.8		0.25
290	0.69		0.43

TABLE VII-continued

Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
291	0.12		0.47
292	100		0.65
293	3175		646
295	3.95		0.18
296	2.2		0.49
297	44		0.11
298	44		0.3
299	1.16		0.44
300	0.29		0.09
301	0.76		0.09
303		24.5	3.87
304		119	161
305		1.24	0.2
306		0.18	0.9
307		0.07	0.4
308		0.48	1.2
318	1220		357

*The binding assays described above may be associated with a margin of error between 10-20%.

Example 3

Human Mu Opioid Receptor Binding Assay

Membranes from Chinese Hamster Ovary cells expressing the human μ opioid receptor (Perkin Elmer #RBHOMM400UA) are homogenized in assay buffer (50 mM Tris, pH 7.5 with 5 mM $MgCl_2$) using a glass tissue grinder, Teflon pestle and a Steadfast Stirrer (Fisher Scientific). The concentration of membranes is adjusted to 300 μg/mL in assay buffer and 100 μL is dispensed into each well of the assay plate, a 96 well round bottom polypropylene plate. Compounds to be tested are solubilized in DMSO (Pierce), 10 mM, then diluted in assay buffer to 6× the desired final concentration. The ligand, ^{3}H-Damgo (Perkin Elmer #NET-902) is also diluted in assay buffer to 3.6 nM. In a second 96 well round bottom polypropylene plate, known as the premix plate, 60 μL of the 6× compound is combined with 60 μL of 3.6 nM ^{3}H-Damgo. From this premix plate 50 μL is transferred to the assay plate containing the membranes, in duplicate. The assay plate is incubated for 2 h at room temperature. A GF/C 96 well filter plate (Perkin Elmer #6005174) is pretreated with 0.3% polyethylenimine for 30 min. The contents of the assay plate are filtered through the filter plate using a Packard Filtermate Harvester, and washed 3 times with 0.9% saline that is 4° C. The filter plate is dried, the underside sealed, and 30 μL Microscint20 (Packard #6013621) added to each well. A Topcount-NXT Microplate Scintillation Counter (Packard) is used to measure emitted energies in the range of 2.9 to 35 KeV. Results are compared to maximum binding, wells receiving no inhibitors. Nonspecific binding is determined in the presence of 1 μM unlabelled Damgo (Tocris #1171). The biological activity of the compounds of the present invention is shown in Table VIII.

The biological activity of the compounds of the present invention may also be measured in a human delta opioid receptor binding assay using the following example.

Example 4

Human Delta Opioid Receptor Binding Assay

This assay is designed to test the ability of a compound to interfere with the binding of tritiated Naltrindole to the

human delta subtype 2 opioid receptor. Membranes from Chinese Hamster Ovary cells expressing the human delta subtype 2 opioid receptor (Perkin Elmer #RBHODM400UA) are homogenized in assay buffer (50 mM Tris, pH 7.5 with 5 mM $MgCl_2$) using a glass tissue grinder, Teflon pestle and a Steadfast Stirrer (Fisher Scientific). The concentration of membranes is adjusted to 100 μg/mL in assay buffer and 100 μL is dispensed into each well of the assay plate, a 96 well round bottom polypropylene plate. Compounds to be tested are solubilized in DMSO (Pierce), 10 mM, then diluted in assay buffer to 6× the desired final concentration. The ligand, ^{3}H-Naltrindole (Perkin Elmer #NET-1065) is also diluted in assay buffer to 6 nM. In a second 96 well round bottom polypropylene plate, known as the premix plate, 60 μL of the 6× compound is combined with 60 μL of 6 nM ^{3}H-Naltrindole. From this premix plate 50 μL is transferred to the assay plate containing the membranes, in duplicate. The assay plate is incubated for 30 min at room temperature. A GF/C 96 well filter plate (Perkin Elmer #6005174) is pretreated with 0.3% polyethylenimine for 30 min. The contents of the assay plate are filtered through the filter plate using a Packard Filtermate Harvester, and washed 3 times with 0.9% saline that is 4° C. The filter plate is dried, the underside sealed, and 30 μL Microscint20 (Packard #6013621) added to each well. A Topcount-NXT Microplate Scintillation Counter (Packard) is used to measure emitted energies in the range of 2.9 to 35 KeV. Results are compared to maximum binding, wells receiving no inhibitors. Nonspecific binding is determined in the presence of 1 μM unlabelled Naltrindole (Sigma #N115).

Biological activity measured for select compounds of the present invention are listed in Table VIII below, including δ- and μ-opioid receptor binding (K_i), as determined using the procedures outlined above.

TABLE VIII

Cpd	hKi δ* (nM)	hKi μ* (nM)
1		3.6
2		2.9
3		13
4		5.5
5		3.9
6		2
7		6.8
8		2.5, 4.4
9		10.9
10		15.5
11		5.1
12		4.1
13		4.8
14		4.7
15		285
16		16
17		2.2
18		1.7
19		18.2
20		63
21		37.6
22		~200
23		34.3
24		9.3
26		17
27		30
28		44
29		38
30		34
31		19
32		6.8
33		6.9
34		19
35		2.8
36		5.6
37		183
38		19
39		0.9
40		152
41		1.6
42		5.8
43		6.9
44		8.7
45		1.2
46		35
47		22
48		0.4
49		48
50		1.4
51	113	2.7
52	66	12.1
53	96	13.1
54	172	1.1
55	44	1.8
56	225	653
57	2.2	0.66
58	70	8.5
59	120	5.1
60	114	2
61	243	3
62	69	2.4
63	473	58
64	1108	117
65	517	0.36
66	550	6.5
67	438	4.5
68	59	0.6
69	272	4.4
70	85	2.6
71	102	0.57
72	71	1.03
73	151	1.9
74	63	9.8
75	8.5	2.6
76	43.1	1.6
77	13.5	1.8
78	28.9	2.4
79	11.5	1.7
80	0.05	1.09
81	15.7	1.7
82	46	2.39
83	48	4.67
84	9.6	1.1
85	1175	5.4
86	400	1
87	38.9	12.6
88	16.2	5.8
89	19.3	9.2
90	6.6	0.7
91	15	4.8
92	5.4	0.25
93	9.5	0.9
94	403	4.1
95	278	7.8
96	14.6	9.7
97	6.3	19.2
98	54	48
99	19.3	16
100	88	20
101	47	24
102	5.2	3.5
103	9.7	23
104	484	100
105	742	410
106	279	150
107	584	2.95
108	43.3	23.5
109	77	8.2
110	1402	191
111	307	6.4
112	135	9.5

TABLE VIII-continued

TABLE VIII-continued

Cpd	hKi δ* (nM)	hKi μ* (nM)
113		16
114	49	1.39
115	321	68
116	30.3	0.54
117	118	0.24
118	316, 212	1.04
119	>10,000	185
120	740	20.8
121	182	25.3
122	107	12.8
123	84	47
124	1279	1.7
125	237	8.6
126	164	7.8
127	710	47
128		58
129		25.3
130	712	1.6
131	675	3.1
132		166
133	108	11.5
134	463	121
135	1040	7
136	1607	726
137		445
138	1183	104
139	1263	58
140	985	79
141	252	52
142	454	8.2
143	69	1.6
144	251	1.3
145	267	
146	71	
147	241	
149	408	
150	992	
151	1295	
152	>10,000	
153	>10,000	
154	>10,000	1
155	345	
156	380	0.59
157	>10,000	2.2
158	>10,000	0.23
159	400	8.6
160	>10,000	>1000
161	>10,000	>1000
162	173	7.6
163	301, 63	0.67
164		16.3
165	322	0.45
166	300, 375	0.39, 0.5
167		4.2
190	285	
191	>10,000	
192		0.62
193	>10,000	
194	103	0.13
195	>10,000	9.8
196		
197		
198	>10,000	140
199	209	0.29
203	501	13.7
204		7.7
205		
206	275.4	
207	132.2	
208		1.2
209		23
210		0.29
211		
212		55
213		>1000

TABLE VIII-continued

Cpd	hKi δ* (nM)	hKi μ* (nM)
214		29
215		1.5
216		
217	506	
218	189	3.92
219		16.2
220		377
221		0.42
222		185
223		
224	81.3	0.65
225		1.4
226		7.91
227		1.92
228		15.9
229		12
231		28
239		
242		2.35
246		5.63
256		2
257		3.4
260		0.58
261		2.58, 1.3
262		3.24
266		69
267		6.88
268		5.79
269		21.5
270		3.27
271		15.5
272		1.93
273		325
274		>1000
289		2.2
303		3.8
304		41

Example 5

Delta Opioid Receptor Functional Assay: [^{35}S]GTPγS Binding Assay in CHO-hδ Cell Membranes, Version 1

Preparation of Membranes

CHO-hδ cell membranes were purchased from Receptor Biology, Inc. (Baltimore, Md.). 10 mg/ml of membrane protein suspended in 10 mM TRIS-HC pH 7.2, 2 mM EDTA, 10% sucrose.

Membranes were maintained at 4-8° C. A portion (1 ml) of membranes was added into 15 mL cold binding assay buffer. The assay buffer contained 50 mM HEPES, pH 7.6, 5 mM $MgCl_2$, 100 mM NaCl, 1 mM DTT and 1 mM EDTA. The membrane suspension was homogenized with a Polytron for 2 times and centrifuged at 3000 rpm for 10 min. The supernent was then centrifuged at 18,000 rpm for 20 min. The pellet was saved in a tube and 10 ml assay buffer was added into the tube. The pellet and buffer were mixed with a Polytron.

Incubation Procedure

The pellet membranes (20 μg/ml) were preincubated with SPA (10 mg/ml) at 25° C. for 45 min in the assay buffer. The SPA (5 mg/ml) coupled with membranes (10 μg/ml) was then incubated with 0.5 nM [^{35}S]GTPγS in the same HEPES buffer containing 50 μM GDP in total volume of 200 μl. Increasing concentrations of receptor agonists were used to stimulate [^{35}S]GTPγS binding. The basal binding was tested

in the absent agonists and no specific binding was tested in the present 10 μM unlabeled GTPγS. The data were analyzed on a Top counter.

Data

The % of Basal=(stimulate−non specific)*100/(basal−non specific). EC50 values were calculated using a Prism program.

Example 6

Delta Opioid Receptor Functional Assay: [^{35}S]GTPγS Binding Assay in NG108-15 Cell Membranes, Version 2

Preparation of Membranes

NG108-15 cell membranes were purchased from Applied Cell Sciences (Rockville, Md.). 8 mg/ml of membrane protein suspended in 10 mM TRIS-HC pH 7.2, 2 mM EDTA, 10% sucrose.

Membranes were maintained at 4-8° C. A portion (1 ml) of membranes was added into 10 ml cold binding assay buffer. The assay buffer contained 50 mM Tris, pH 7.6, 5 mM $MgCl_2$, 100 mM NaCl, 1 mM DTT and 1 mM EGTA. The membrane suspension was homogenized with a Polytron for 2 times and centrifuged at 3000 rpm for 10 min. The supernent was then centrifuged at 18,000 rpm for 20 min. The pellet was saved in a tube and 10 ml assay buffer was added into the tube. The pellet and buffer were mixed with a Polytron.

Incubation Procedure

The pellet membranes (75 μg/ml) were preincubated with SPA (10 mg/ml) at 25° C. for 45 min in the assay buffer. The SPA (5 mg/ml) coupled with membranes (37.5 μg/ml) was then incubated with 0.1 nM [^{35}S] GTPγS in the same Tris buffer containing 100 μM GDP in total volume of 200 μl. Increasing concentrations of receptor agonists were used to stimulate [^{35}S] GTPγS binding. The basal binding was tested in the absent agonists and no specific binding was tested in the present 10 μM unlabeled GTPγS. The data were analyzed on a Top counter.

Data Analysis

The following parameters were calculated:

$$\%\ \text{Stimulation} = \frac{(\text{test compound } cpm - \text{non-specific } cpm)}{(\text{Basal } cpm - \text{non-specific } cpm)} \times 100.$$

% Inhibition=(% stimulation by 1 μM SNC80−% stimulation by 1 μM SNC80 in presence of test compound)×100/(% Stimulation by 1 μM SNC80−100)

% of Basal=(stimulate−non specific)*100/(basal−non specific).

EC_{50} values were calculated using GraphPad Prism.

Example 7

Mu Opioid Receptor Functional Assay: [^{35}S]GTPγS Binding Assays in CHO-hMOR cell membranes, Versions 1 and 2

CHO-hMOR cell membranes were purchased from Receptor Biology, Inc. (Baltimore, Md.). About 10 mg/ml of membrane protein was suspended in 10 mM TRIS-HCl pH 7.2, 2 mM EDTA, 10% sucrose, and the suspension kept on ice. One ml of membranes was added to 15 ml cold binding assay buffer containing 50 mM HEPES, pH 7.6, 5 mM $MgCl_2$, 100 mM NaCl, 1 mM DTT and 1 mM EDTA. The membrane suspension was homogenized with a Polytron and centrifuged at 3,000 rpm for 10 min. The supernatant was then centrifuged at 18,000 rpm for 20 min. The pellet was resuspended in 10 ml assay buffer with a Polytron.

The membranes were preincubated with wheat germ agglutinin coated SPA beads (Amersham) at 25° C. for 45 min in the assay buffer. The SPA bead (5 mg/ml) coupled membranes (10 μg/ml) were then incubated with 0.5 nM [^{35}S] GTPγS in the assay buffer. The basal binding is that taking place in the absence of added test compound; this unmodulated binding is considered as 100%, with agonist stimulated binding rising to levels significantly above this value. A range of concentrations of receptor agonists was used to stimulate [^{35}S]GTPγS binding. Both basal and non-specific binding was tested in the absence of agonist; non-specific binding determination included 10 μM unlabeled GTPγS.

Compounds were tested for function as antagonists by evaluating their potential to inhibit agonist-stimulated GTPγS binding. Radioactivity was quantified on a Packard Top-Count. The following parameters were calculated:

$$\%\ \text{Stimulation} = \frac{(\text{test compound } cpm - \text{non-specific } cpm)}{(\text{Basal } cpm - \text{non-specific } cpm)} \times 100.$$

% Inhibition=(% stimulation by 1 μM SNC80−% stimulation by 1 μM SNC80 in presence of test compound)×100/(% Stimulation by 1 μM SNC80−100)

EC_{50} values were calculated using GraphPad Prism.

Biological activity measured for select compounds of the present invention are listed in Table VIII below, including δ- and μ-opioid receptor functional data (% I and EC50), as determined from a single set of experiments using the procedures outlined above.

TABLE IX

Cpd No.	DOR GTP-binding Assay_v1 EC50 (nM)	DOR GTP-binding Assay_v2_EC50 (nM)	DOR GTP-binding Assay v2 (% I)	MOR GTP binding assay v2 EC50 (nM)	MOR GTP binding assay_v2 (% I)	MOR GTP assay_v1% of Basal	MOR GTP binding assay_v1 (% I)
1		88	22.10				
4		46	66.12				
5		>10,000	47.12	71	7.87		
8		>10,000	94.03	1.2	13.95		
9		3.4	67.13				
14		0.6	59.70				

TABLE IX-continued

Cpd No.	DOR GTP-binding Assay_v1 EC50 (nM)	DOR GTP-binding Assay_v2_EC50 (nM)	DOR GTP-binding Assay v2 (% I)	MOR GTP binding assay v2 EC50 (nM)	MOR GTP binding assay_v2 (% I)	MOR GTP assay_v1% of Basal	MOR GTP binding assay_v1 (% I)
17		1.3	68.64	2.5	8.71		
18		>10,000	100				
18				1.0	7.54		
20		>10,000	78.74				
29		>10,000	79.05				
48		>10,000	108.36	2.2	24.53		
50		1.4	60.27				
51		27	66.04				
75		1.4	65.35				
114	35					717.59	13.20
117	37					816.16	3.31
122						278.08	41.93
130	16					866.39	1.62
131	99					391.98	28.64
146	27					740.77	2.79
147	51					779.35	1.00
149	44					753.53	1.00
150	49					476.63	53.35
151	350					606.38	24.19
155	150					655.93	14.32
163	21					1286.00	1.00
164	2500					1077.00	1.00
165	231					1182.00	1.00
166	21					1448.00	1.00
166	71					1425.00	1.00
167						780.00	17.00
170	115					1031.00	26.00
173						147.00	85.00
174	20					864.00	42.00
175						471.00	53.00
177						625.00	23.00
178						1059.00	10.00
181						1304.00	1.00
182						1091.00	6.00
183	2320					962.00	27.00
184						862.00	13.00
190	3830					109, 194	70.00
192	76					385.00	30.00
193						182.00	54.00
194	189					558.00	1.00
195						378.00	34.00
196	24					620.00	1.00
197	140					587.00	1.00
199	217					465.00	11.00
202	1580					529.00	1.00
203	515					331.00	20.00
205	32					566.00	1.00
206	37					446.00	1.00
207	8.65					432, 1160	40.00
207	12					1183.00	21.00
208						475.00	1.00
209						295.00	10.00
210						414.00	10.00
211						371.00	10.00
214	26000					295.00	3.00
215	1060					606.00	1.00
216	16					666.00	1.00
217	82					599.00	1.00
218	20					599.00	1.00
219	3560					611.00	1.00
221	308					427.00	13.00
223	56					495.00	1.00
224	103					694.00	1.00
225	2190					657.00	1.00
226		>10,000	19.71				
227		>10,000	66.56	60.8	36.00		
230			48.93				
239		>10,000					
242		>10,000	91.45				
246		0.3	47.01	4.5	21.30		
247		44	41.89				
248		15	31.72				
249		8	20.14				
250		10	34.93				
251		18	53.94				

TABLE IX-continued

Cpd No.	DOR GTP-binding Assay_v1 EC50 (nM)	DOR GTP-binding Assay_v2_EC50 (nM)	DOR GTP-binding Assay v2 (% I)	MOR GTP binding assay v2 EC50 (nM)	MOR GTP binding assay_v2 (% I)	MOR GTP assay_v1% of Basal	MOR GTP binding assay_v1 (% I)
252		32.1	66.00	4.15	24.00		
253		1.35	52.00	251	28.00		
254		6.27	62.00	316	42.00		
255		13.1	54.00	3.48	33.00		
256		>10,000	89.19	13	29.40		
257		7.4	48.88	3.9	10.96		
260		>10,000	100.97	1.5	2.89		
261		21	30.04	17	5.88		
267		6	31.76				
269		86	21.18	48	1.00		
270		1000	63.51	56	6.61		
275		3	72.08				
286		2.6	34.65				
287		>10,000	84.50				
288		>10,000	74.54				
289		>10,000	86.27				
290		>10,000	52.41				
291		>10,000	96.52				
295		2.2	71.66	1.4	8.21		
296		7.9	69.41	2.2	9.35		
299		2.3		1.0	12.11		
300		32		2.6	15.40		
301		>10,000	109.56	2.6	76.20		
303		95	23.85	30	1.00		
309				23.0	47.00		
310				3920	51.00		
311		1.02	41.00				
312				58.7	35.00		
313		5.03	49	50.6	29.00		
316				24.1	76		

Example 8

In Vivo Assay

Stress-Induced Fecal Output (Fecal Output for 1 Hr)

This assay evaluates the fecal output in novel environment-stressed mice to that of acclimated controls.

Methods: Adult, male, Crl:CD-1 (ICR) mice, weighing ~30-35 g were used in these studies, with a minimum of 10 mice per dose group. One group of mice was assigned as acclimated, or "non-stressed" controls. These control mice were transported from colony housing, where they were housed 3/cage in polycarbonate cages with access to food and water ad lib. to the procedure room. The mice were removed from their home cages and individually housed in 20 cm wide×20 cm deep×15 cm tall cages, equipped with a wire mesh bottom where they remained for a 16-18 hr period of acclimation to their novel environment. Mice were allowed access to food and water ad lib. during acclimation. The other groups of mice were assigned as non-acclimated, or "stressed" treatment groups. Each mouse in each group was weighed and vehicle, or test compound, was intragastrically administered by oral intubation in 0.5% methylcellulose. Mice were allowed access to water only ad lib. during the test period. After compound administrations, acclimated (control) as well as non-acclimated (stressed) mice were individually housed in a 20 cm wide×20 cm deep×15 cm tall cage, with a wire mesh bottom. An absorbant cardboard is placed beneath the cages. The number of fecal pellets excreted by each mouse was determined at hourly intervals following placement of the mice in the individual cages. Raw Data=# of fecal pellets/mouse/hr. The mean fecal pellet output for each test group was calculated and the results expressed as a percent of the mean fecal pellet output of the control group (the acclimated, non-stressed group, to which vehicle only was administered). ANOVA was performed and Tukey's Multiple Comparison Test used to compare the means, which were considered significantly different when $P<0.05$. Data is shown in Table X, XI, and XII.

TABLE X

		Fecal Output (# pellets)					
Cpd No.	dose (mg/kg)	control	NES	cpd	NES % ctrl	cpd % control	cpd % NES
18	30	2.3	3.8	3.1	166.7	137.8	82.7
50	30	2.3	7.0	3.3	304.3	143.5	47.1
55	30	3.9	14.1	8.3	361.5	212.8	58.9
57	30	3.9	14.1	7.6	361.5	194.9	53.9
58	30	2.3	7.0	3.9	304.3	169.6	55.7
75	30	3.1	9.1	6.4	293.5	206.5	70.3
75	30	1.9	3.9	1.4	206.7	73.3	35.5
78	30	3.6	7.3	3.3	202.8	91.7	45.2
79	30	3.6	7.3	7.1	202.8	197.2	97.3
80	30	3.6	7.3	5.5	202.8	152.8	75.3
80	30	3.9	13.1	10.3	335.9	264.1	78.6
85	30	5.4	12.0	7.9	222.2	146.3	65.8
87	30	7.3	12.9	10.3	176.7	141.1	79.8
89	30	5.0	11.6	6.4	232.0	128.0	55.2
90	30	3.1	12.9	10.3	416.1	332.3	79.8
91	30	3.1	12.9	8.9	416.1	287.1	69.0
92	30	3.6	11.1	9.2	308.3	255.6	82.9
93	30	3.6	11.1	5.0	308.3	138.9	45.0
94	30	2.7	9.1	9.4	337.0	348.1	103.3
95	30	2.7	9.1	8.5	337.0	314.8	93.4
97	30	7.3	12.9	4.8	176.7	65.8	37.2
102	30	5.7	15.0	3.4	263.2	59.6	22.7
103	30	7.3	12.9	10.2	176.7	139.7	79.1
107	30	5.7	15.0	13.1	263.2	229.8	87.3
111	30	7.2	10.3	4.4	143.1	60.8	42.5
112	30	7.2	10.3	7.2	143.1	100.0	69.9

TABLE X-continued

Fecal Output (# pellets)							
Cpd No.	dose (mg/kg)	control	NES	cpd	NES % ctrl	cpd % control	cpd % NES
114	30	7.2	10.3	7.8	143.1	108.3	75.7
118	30	5.4	12.0	7.2	222.2	133.7	60.2
133	30	5.5	12.1	9.9	220.0	180.0	81.8
143	10	3.7	13.6	9.1	367.6	245.9	66.9
143	30	7.5	9.2	5.2	122.7	69.3	56.5
144	30	3.7	13.6	11.5	367.6	310.8	84.6
178	30	3.2	8.8	5.5	275.0	171.9	62.5
192	10	5.4	12.5	10.5	231.5	194.4	84.0
194	10	5.4	12.5	11.8	231.5	218.5	94.4
194	30	8.1	11.0	4.2	135.8	51.9	38.2
194	30	3.1	4.8	4.9	154.3	157.5	102.1
194	30	3.7	14.0	6.2	378.4	167.6	44.3
196	10	3.7	14.0	9.2	378.4	248.6	65.7
196	30	1.1	9.5	4.3	863.6	390.9	45.3
199	10	2.7	10.5	9.1	388.9	337.0	86.7

TABLE X-continued

Fecal Output (# pellets)							
Cpd No.	dose (mg/kg)	control	NES	cpd	NES % ctrl	cpd % control	cpd % NES
199	10	3.8	13.1	10.8	344.7	284.2	82.4
205	30	3.3	9.5	2.3	287.9	70.7	24.6
206	10	3.8	13.1	8.6	344.7	226.3	65.6
207	10	5.6	9.4	8.3	167.9	148.2	88.3
207	10	7.7	13.0	5.0	168.8	64.9	38.5
207	10	5.7	12.8	6.6	225.9	116.5	51.6
207	10	2.9	12.8	5.3	441.4	182.8	41.4
207	30	3.5		3.2		91.4	
207	30	3.5	13.0	6.4	371.4	184.1	49.6
216	10	3.6	10.3	4.9	286.1	136.1	47.6
218	30	2.7	10.5	3.7	388.9	137.6	35.4
223	30	3.1	4.8	5.0	154.3	160.7	104.2
224	10	3.6	6.9	3.5	191.7	97.2	50.7
225	30	3.1	4.8	7.3	154.3	234.7	152.1

TABLE XI

Dose-dependent Mouse Fecal Pellet Output Test

	# of pellets			Compound (mg)							
Cpd No.	control	NES	NES (% ctrl)	0.3	0.5	1.0	3.0	5.0	6.0	10.0	30.0
75			235.7								
93	2.7	8.3	307.4				6.2			5.5	3.2
97	6.1	11.6	190.2				14			7.5	3.5
97	4.8	10.1	210.4				9.1			10.4	2.3
102	5.3	10.7	201.9				6.9			4.5	2.22
114	3.4	10	294.1				9.6			7.7	5.4
200	3.556	8.8	247.5				8.1			8.2	5.8
207	5.2	11.4	219.2	11.4			12			4.9	
207	4.8	8.6	179.2		9.4			8.6		6.7	
207	3.4	10.8	317.6						7.5	5.5	3.5
207	3.6	6.5	180.6				7.3			4.8	3.4
224	2.2	9.6	436.4			7.6	7.2			4.2	

TABLE XII

Dose-dependent Mouse Fecal Pellet Output Test: Computed Results

Cpd	Compound (% control)								Compound (% NES)							
No.	0.3	0.5	1.0	3.0	5.0	6.0	10.0	30.0	0.3	0.5	1.0	3.0	5.0	6.0	10.0	30
75				223.8			188.1	100								
93				229.6			203.7	119				74.7			66.27	38.55
97				226.2			123.0	57				119			64.66	30.17
97				189.6			216.7	48				90.1			103	22.77
102				130.2			84.9	42				64.5			42.06	20.77
114				282.4			226.5	159				96			77	54
200				227.8			230.6	163				92.05			93.18	65.91
207	219.2			228.8			94.2		100			104.4			42.98	
207		195.8			179.2		139.6			109			100		77.91	
207						220.6	161.8	103						69.44	50.93	32.41
207				202.8			133.3	94				112.3			73.85	52.31
224			345.5	327.3			190.9				79.17	75			43.75	

Example 9

In Vivo Assay

Stress-Induced Entire GI Tract Transit (6 Hour Transit Time Test)

Methods: The animals used in these studies are male CD-1 mice, ave. wt. ~30 g. Procedure: Mice were housed in LAM under 12 h/12 h light/dark cycle, food & water ad lib. On the day before the experiments, the mice assigned to the "acclimated" (non-stressed) control group were placed into individual wire mesh-bottomed cages, provided food and water ad lib. The acclimated control group was in this new environment for 16-18 hrs prior to beginning the test. On the day of the experiment, mice assigned to experimental groups were housed in home cages were transported to procedure room and remain in their home cages until the start of the transit portion of the study. Mice were intragastrically dosed with compounds (volume remains constant at 0.1 mL/10 g body wt) by oral gavage 30 minutes before carmine (a red vital dye that does not have the drug-adsorbing properties of charcoal) is administered (0.25 mL, 6% carmine in 0.5% methylcellulose). After the carmine marker was administered each mouse was placed in the novel environment cage. One hour after administration of carmine, the fecal pellet output of each animal was recorded. At one-hour intervals thereafter the fecal pellets were examined for the presence of carmine-dye. The number of mice that excreted a carmine-containing fecal pellet at the end of each hour post carmine administration was recorded, until all mice had excreted carmine in a fecal pellet or the end of 6 hrs post carmine administration, whichever occurred first. A variant of this novel environment stress (NES) paradigm is to use the same procedures of dye and compound administrations, but to use restraint (confinement in a small plastic tube for 3 hr) as a stressor (RS=restraint stress), followed by two hours in an individual cage (total of 5 hr fecal transit time). Data is shown in Table XIII. The original data are quantal, i.e. a mouse in the treatment group either did, or did not exhibit entire GI tract transit (excrete colored feces). The mouse entire GI tract (MEGIT) transit test can thus be done in mice that are all acclimated (non-stressed), in which case the data are expressed as % control (vehicle only), or in mice that are exposed to NES or RS, in which cases the data are expressed as % of the vehicle treated NES or RS group. Data is shown in Table XIII.

TABLE XIII

Mouse entire GI tract transit test (MEGIT or MEGIT-NES or MEGIT-RS*)

Cpd No.	dose (mg)	route	MEGIT-NES Entire GI transit 6 hr (% NES)	MEGIT entire GI transit 6 hr % ctrl	MEGIT-RS entire GI transit 5 hr (% RS)
4	20	p.o.			100
18	30	p.o.	80		
75	30	p.o.		125	
75	60	p.o.		0	
75	100	p.o.		0	
227	20	p.o.			100
242	20	p.o.			100
261	20	p.o.			103.6
270	20	p.o.			112.5
289	20	p.o.			14.1

*RS = restraint stress;
NES = novel environment stress

Example 10

In Vivo Assay

Upper GI Tract Transit

Methods: The animals used in these studies were male CD-1 mice, ave. wt. ~30 g. Mice were housed under 12 h/12 h light/dark cycle, food & water ad lib. On the day of the experiment mice were assigned to experimental groups, including one vehicle-only group (=control). At 30 min before administration of carmine dye, animals were dosed with vehicle or vehicle-plus-compound, mice were returned to their home cages after drug administration. After administration of carmine, the animals were either returned to their home cages (non-stressed) or individually placed in the same metal cages as used in the fecal output or entire GI tract transit to induce a novel environment stress. One hour after administration of carmine, mice were sacrificed by cervical dislocation, the abdomen opened midventrally, the small intestine from pylorus to cecum was removed, the mesentery divided in order to lay the intestine straight & flat—without stretching. The total length of intestine and the length of carmine-dyed intestine were measured in order to determine the percent of the upper GI tract over which transit had occurred as follows: {(Length of carmine-dyed intestine)/(Total length of intestine)}×100=% upper GI transit. The data expressed were group means±SD (or s.e.m.) and data expressed as % of control. Statistics: ANOVA with the Tukey-Kramer post-hoc test and means were considered significantly different when $P<0.05$. Data is presented in Table XIV.

TABLE XIV

Mouse Upper GI Transit Test (MUGIT)

Cpd No.	dose (mg)	route	upper GI transit (% ctrl)
8	30	p.o.	77.3
17	30	p.o.	37.3
18	10	p.o.	99.6
18	50	p.o.	69.9
18	5	p.o.	94.2
18	25	p.o.	83.0
18	100	p.o.	41.2
18	30	p.o.	37.5
18	30	p.o.	53.1
48	30	p.o.	102.1
75	30	p.o.	71.1
75	60	p.o.	56.0
75	100	p.o.	45.6
227	30	p.o.	93.9
256	30	p.o.	89.7
261	30	p.o.	87.7
270	30	p.o.	96.5
287	30	p.o.	66.4
289	30	p.o.	76.4
315	30	p.o.	94.5

Example 11

Visceral Hyperalgesia Testing

Method: Rats were chronically instrumented with EMG electrodes in the muscles of the anterior abdominal wall. Distention of an intracolonic balloon, using a barostat apparatus, evoked increases in the EMG recordings that are related to the pressure. Control responses are compared with repeat stimulation 4 hours after zymosan is administered to the

colon (FIG. 1). Animals with 10% higher visceromotor responses for at least two distending pressures are considered to exhibit visceral hyperalgesia.

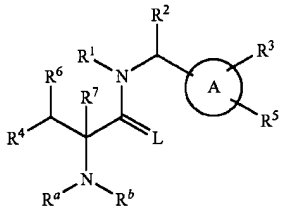
Compound 18 in 5 rats at repeated distentions of 40 mmHg administered at 30 mg/kg, i.p., blocked the hyperalgesic response to colorectal balloon distention following zymosan (FIG. 2 and FIG. 3).

The agonistic or antagonistic activity of the compounds of the invention at the kappa opioid receptor can be determined by known methods, for example, by the procedure described in S. Giuliani, A. Lecci, M. Tramontana, C. A. Maggi, Role of kappa opioid receptors in modulating cholinergic twitches in the circular muscle of guinea-pig colon. *Brit J Pharmacol* 119, 985-9 (November, 1996).

What is claimed is:

1. A method for treating or pain or gastrointestinal disorder, wherein said pain is centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, pain related to inflammation, progressive disease related pain, neuropathic pain, acute pain, or chronic pain, and wherein said gastrointestinal disorder is ulcerative colitis, Crohn's disease, diarrhea-predominant irritable bowel syndrome, or alternating irritable bowel syndrome, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Formula (I)

Formula (I)



wherein:

R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, cycloalkyl, heterocyclyl, aryl(C_{1-6})alkyl, and heteroaryl(C_{1-6})alkyl; wherein when R^1 is phenyl(C_{1-6})alkyl, phenyl is optionally fused to a heterocyclyl or cycloalkyl;

wherein when R^1 is C_{1-2}alkyl, said C_{1-2}alkyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkoxy, aryl, cycloalkyl, heterocyclyl, hydroxy, cyano, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, trifluoromethyl, and carboxy;

and further, wherein when R^1 is C_{3-6}alkyl, said C_{3-6}alkyl is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkoxy, aryl, cycloalkyl, heterocyclyl, hydroxy, cyano, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, trifluoromethyl, and carboxy;

wherein the cycloalkyl and heterocyclyl of C_{1-2}alkyl and C_{3-6}alkyl are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, hydroxy, cyano, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, trifluoromethyl, carboxy, aryl(C_{1-6})alkoxycarbonyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$-aminocarbonyl, and aminosulfonyl;

furthermore, wherein the cycloalkyl and heterocyclyl of R^1 are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, hydroxy, cyano, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, trifluoromethyl, carboxy, aryl(C_{1-6})alkoxycarbonyl, C_{1-6}alkoxycarbonyl, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, and aminosulfonyl;

furthermore, wherein the aryl and heteroaryl portion of the R^1 substituents aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl, are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-6}alkyl; hydroxy(C_{1-6})alkyl; C_{1-6}alkoxy; C_{6-10}aryl(C_{1-6})alkyl; C_{6-10}aryl(C_{1-6})alkoxy; C_{6-10}aryl; heteroaryl optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, and carboxy; cycloalkyl; heterocyclyl; C_{6-10}aryloxy; heteroaryloxy; cycloalkyloxy; heterocyclyloxy; amino; C_{1-6}alkylamino; (C_{1-6}alkyl)$_2$-amino; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-6})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; heterocyclylcarbonyl; carboxy; C_{1-6}alkoxycarbonyl; C_{1-6}alkoxycarbonyloxy; C_{1-6}alkylcarbonyl; C_{1-6}alkylcarbonylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl; (C_{1-6}alkyl)$_2$aminocarbonyl; cyano; halogen; trifluoromethyl; trifluoromethoxy; and hydroxy;

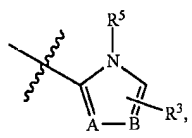
provided that no more than one R^{11} substituent is selected from the group consisting of C_{6-10}aryl(C_{1-6})alkyl; C_{6-10}aryl(C_{1-6})alkoxy; C_{6-10}aryl; heteroaryl optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, and carboxy; cycloalkyl; heterocyclyl; C_{6-10}aryloxy; heteroaryloxy; cycloalkyloxy; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4} alkoxycarbonyl; heterocyclylcarbonyl, and heterocyclyloxy;

R^2 is hydrogen, C_{1-8}alkyl, hydroxy(C_{1-8})alkyl, C_{6-10}aryl(C_{1-6})alkoxy(C_{1-6})alkyl, or C_{6-10}aryl(C_{1-8})alkyl;

wherein the C_{6-10}aryl group in the C_{6-10}aryl-containing substituents of R^2 are optionally substituted with one to two substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$-amino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, cyano, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy; and, wherein the C_{1-6}alkyl and C_{1-6}alkoxy substituents of aryl are optionally substituted with hydroxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, or aryl;

A is a-1, optionally substituted with R^3 and R^5;

a-1



wherein

A-B is N-C;

R^3 is one to two substituents independently selected from the group consisting of C_{1-6}alkyl, aryl, aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, heteroaryl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkenyl, heteroaryl

(C_{2-6})alkynyl, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, arylamino, heteroarylamino, aryloxy, heteroaryloxy, trifluoromethyl, and halogen;

wherein the aryl, heteroaryl, and the aryl and heteroaryl of aryl(C_{1-6})alkyl, aryl(C_{2-6})alkenyl, aryl(C_{2-6})alkynyl, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkenyl, heteroaryl(C_{2-6})alkynyl, arylamino, heteroarylamino, aryloxy, and heteroaryloxy, are optionally substituted with one to five fluoro substituents or one to three substituents independently selected from the group consisting of C_{1-6}alkyl, hydroxy(C_{1-6})alkyl, C_{1-6}alkoxy, C_{6-10}aryl(C_{1-6})alkyl, C_{6-10}aryl(C_{1-6})alkoxy, C_{6-10}aryl, C_{6-10}aryloxy, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkoxy, heteroaryl, heteroaryloxy, C_{6-10}arylamino, heteroarylamino, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, carboxy(C_{1-6})alkylamino, carboxy, C_{1-6}alkylcarbonyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylcarbonylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, (C_{1-6}alkyl)$_2$aminocarbonyl, carboxy(C_{1-6})alkylaminocarbonyl, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxy, C_{1-6}alkylsulfonyl, and C_{1-6}alkylsulfonylamino; provided that no more than one such substituent on the aryl or heteroaryl portion of R^3 is selected from the group consisting of C_{6-10}aryl(C_{1-6})alkyl, C_{6-10}aryl(C_{1-6})alkoxy, C_{6-10}aryl, C_{6-10}aryloxy, heteroaryl(C_{1-6})alkyl, heteroaryl(C_{1-6})alkoxy, heteroaryl, heteroaryloxy, C_{6-10}arylamino, heteroarylamino;

and wherein C_{1-6}alkyl and C_{1-6}alkyl of aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl are optionally substituted with a substituent selected from the group consisting of hydroxy, carboxy, C_{1-4}alkoxycarbonyl, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, aminocarbonyl, (C_{1-4})alkylaminocarbonyl, di(C_{1-4}alkylaminocarbonyl, aryl, heteroaryl, arylamino, heteroarylamino, aryloxy, heteroaryloxy, aryl(C_{1-4})alkoxy, and heteroaryl(C_{1-4})alkoxy;

R^4 is C_{6-10}aryl or a heteroaryl selected from the group consisting of furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, isoindolyl, indolinyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, quinolizinyl, quinolinyl, isoquinolinyl and quinazolinyl;

wherein R^4 is optionally substituted with one to three R^{41} substituents independently selected from the group consisting of (C_{1-6})alkyl optionally substituted with amino, C_{1-6}alkylamino, or (C_{1-6}alkyl)$_2$amino; (C_{1-6})alkoxy; phenyl(C_{1-6})alkoxy; phenyl(C_{1-6})alkylcarbonyloxy wherein C1-6 alkyl is optionally substituted with amino; a non fused 5-membered-heteroaryl(C_{1-6})alkylcarbonyloxy; a non fused 5-membered-heteroaryl; hydroxy; halogen; aminosulfonyl; formylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl wherein (C_{1-6})alkyl is optionally substituted with amino, C_{1-6}alkylamino, or (C_{1-6}alkyl)$_2$amino; (C_{1-6}alkyl)$_2$aminocarbonyl wherein each (C_{1-6})alkyl is optionally substituted with amino, C_{1-6}alkylamino, or (C_{1-6}alkyl)$_2$amino; heterocyclylcarbonyl wherein heterocyclyl is a 5-7 membered nitrogen-containing ring and said heterocyclyl is attached to the carbonyl carbon via a nitrogen atom; carboxy; or cyano; and wherein the phenyl portion of phenyl(C_{1-6})alkylcarbonyloxy is optionally substituted with (C_{1-6})alkyl (C_{1-6})alkoxy, halogen, cyano, amino, or hydroxy;

provided that no more than one R^{41} is C_{1-6}alkyl substituted with C_{1-6}alkylamino or (C_{1-6}alkyl)$_2$amino; aminosulfonyl; formylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl; (C_{1-6}alkyl)$_2$aminocarbonyl; heterocyclylcarbonyl; hydroxy; carboxy; or a phenyl- or heteroaryl-containing substituent;

R^5 is a substituent on a nitrogen atom of ring A selected from the group consisting of hydrogen and C_{1-4}alkyl;

R^6 is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen or C_{1-6}alkyl;

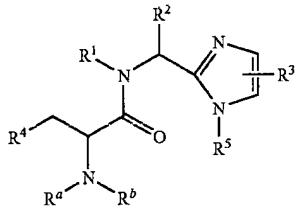
R^a and R^b are independently selected from the group consisting of hydrogen, C_{1-6}alkyl, and C_{1-6}alkoxycarbonyl; alternatively, when R^a and R^b are each other than hydrogen, R^a and R^b are optionally taken together with the nitrogen atom to which they are both attached to form a five to eight membered monocyclic ring;

L is selected from the group consisting of O, S, and N(R^d) wherein R^d is hydrogen of C_{1-6}alkyl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

2. A method for treating or ameliorating pain or gastrointestinal disorder, wherein said pain is selected from the group consisting of centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, pain related to inflammation, progressive disease related pain, neuropathic pain, acute pain, and chronic pain, and wherein said gastrointestinal disorder is selected from the group consisting of ulcerative colitis, Crohn's disease, diarrhea-predominant, irritable bowel syndrome, and alternating irritable bowel syndrome, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Formula (1a)

Formula (Ia)



wherein:

R^1 is selected from the group consisting of phenyl(C_{1-3})alkyl, pyridinyl(C_{1-3})alkyl, and furanyl(C_{1-3})alkyl; wherein phenyl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of is C_{1-3}alkoxy; tetrazolyl, C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; chloro; fluoro; trifluoromethoxy; methoxycarbonyl; and carboxy; provided that no more than one R^{11} is C_{6-10}arylaminocarbonyl;

R^2 is hydrogen or methyl;

R^3 is one to two substituents independently selected from the group consisting of methyl and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro and carboxy;

R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two substituents independently selected from the group consisting of methyl, methoxy, and benzyloxy;

R^5 is hydrogen;

R^a and R^b are each hydrogen;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

3. The method of claim **1** wherein the chronic pain is selected from the group consisting of neuropathic pain conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes and cluster or migraine headaches.

4. The method of claim **2** wherein the chronic pain is selected from the group consisting of neuropathic pain conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes and cluster or migraine headaches.

5. The method of claim **1** wherein R^1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, aryl(C_{1-4})alkyl, and heteroaryl(C_{1-4})alkyl;

wherein the aryl and heteroaryl portion of aryl(C_{1-4})alkyl and heteroaryl(C_{1-4})alkyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-6}alkoxy; heteroaryl optionally substituted with one to two substitutents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, and carboxy; carboxy; C_{1-4}alkoxycarbonyl; C_{1-4}alkoxycarbonyloxy; aminocarbonyl; C_{1-4}alkylaminocarbonyl; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-6})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; heterocyclylcarbonyl; cyano; halogen; trifluoromethoxy; and hydroxy; provided that no more than one R^{11} is heteroaryl (optionally substituted with one to two C_{1-4}alkyl substituents); C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; or heterocyclylcarbonyl.

6. The method of claim **1** wherein R^1 is selected from the group consisting of C_{6-10}aryl(C_{1-4})alkyl, pyridinyl(C_{1-4})alkyl, and furanyl(C_{1-4})alkyl; wherein C_{6-10}aryl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-3}alkoxy; tetrazolyl; carboxy; C_{1-4}alkoxycarbonyl; aminocarbonyl; C_{1-4}alkylaminocarbonyl; C_{1-3}alkylaminocarbonyl; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; cyano; halogen; and trifluoromethoxyl; provided that no more than one R^{11} is C_{6-10}arylaminocarbonyl.

7. The method of claim **1** wherein R^1 is selected from the group consisting of phenyl(C_{1-3})alkyl, pyridinyl(C_{1-3})alkyl, and furanyl(C_{1-3})alkyl; wherein phenyl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-3}alkoxy; tetrazolyl, C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; chloro; fluoro; trifluoromethoxy; C_{1-4}alkoxycarbonyl; and carboxy; provided that no more than one R^{11} is C_{6-10}arylaminocarbonyl.

8. The method of claim **1** wherein R^1 is phenylmethyl, pyridinylmethyl, or furanylmethyl; wherein phenyl, pyridinyl, and (uranyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of methoxy; tetrazolyl; cyclopropylaminocarbonyl; (2-hydroxyeth-1-yl)aminocarbonyl; methoxycarbonyl; phenylaminocarbonyl wherein phenyl is optionally substituted with carboxy; morpholin-4-ylcarbonyl; and carboxy.

9. The method of claim **1** wherein R^2 is a substituent selected from the group consisting of hydrogen, C_{1-4}alkyl, hydroxy(C_{1-4})alkyl, and phenyl(C_{1-6})alkoxy(C_{1-4}alkyl;

wherein said phenyl is optionally substituted with one to two substituents independently selected from the group consisting of C_{1-3}alkyl, C_{1-3}alkoxy, hydroxy, cyano, fluoro, chloro, bromo, trifluoromethyl, and trifluoromethoxy.

10. The method of claim **1** wherein R^2 is a substituent selected from the group consisting of hydrogen and C_{1-4}alkyl.

11. The method of claim **1** wherein R^2 is hydrogen or methyl.

12. The method of claim **1** wherein R^3 is one to two substituents independently selected from the group consisting of C_{1-6}alkyl, halogen, and aryl;

wherein aryl is optionally substituted with one to three substituents independently selected from the group consisting of halogen, carboxy, aminocarbonyl, C_{1-3}alkylsulfonylamino, cyano, hydroxy, amino, C_{1-3}alkylamino, and $(C_{1-3}alkyl)_2$amino.

13. The method of claim **1** wherein R^3 is one to two substituents independently selected from the group consisting of C_{1-3}alkyl, bromo, and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro, fluoro, iodo, carboxy, aminocarbonyl, and cyano.

14. The method of claim **1** wherein R^3 is one to two substituents independently selected from the group consisting of methyl and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro and carboxy.

15. The method of claim **1** wherein at least one R^3 substituent is phenyl.

16. The method of claim **1** wherein R^3 is a substituent selected from the group consisting of methyl and phenyl; wherein phenyl is optionally substituted with one to two substituents independently selected from the group consisting of chloro and carboxy.

17. The method of claim **1** wherein R^4 is C_{6-10}aryl optionally substituted with one to three R^{41} substituents independently selected from the group consisting of (C_{1-3})alkyl, (C_{1-6})alkoxy, phenyl(C_{1-6})alkoxy; hydroxy; halogen; formylamino; aminocarbonyl; C_{1-6}alkylaminocarbonyl; $(C_{1-6}alkyl)_2$aminocarbonyl; heterocyclylcarbonyl wherein heterocyclyl is a 5-7 membered nitrogen-containing ring and said heterocyclyl is attached to the carbonyl carbon via a nitrogen atom; carboxy; and cyano;

provided that no more than one R^{41} substituent is formylamino, aminocarbonyl, C_{1-6}alkylaminocarbonyl, $(C_{1-6}alkyl)_2$aminocarbonyl, heterocyclylcarbonyl, hydroxy, carboxy, or a phenyl-containing substituent.

18. The method of claim **1** wherein R^4 is phenyl substituted with one to three R^{41} substituents independently selected from the group consisting of (C_{1-3})alkyl, (C_{1-3})alkoxy, phenyl(C_{1-3})alkoxy, hydroxy, C_{1-6}alkylaminocarbonyl, and aminocarbonyl; provided that no more than one R^{41} substituent is aminocarbonyl, C_{1-6}alkylaminocarbonyl, hydroxy, or a phenyl-containing substituent.

19. The method of claim **1** wherein R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two substituents independently selected from the group consisting of methyl, methoxy, and benzyloxy.

20. The method of claim **1** wherein R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two methyl substituents.

21. The method of claim 1 wherein R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and substituted at the 2- and 6-positions with methyl substituents.

22. The method of claim 1 wherein R^5 is hydrogen or methyl.

23. The method of claim 1 wherein R^5 is hydrogen.

24. The method of claim 1 wherein R^6 is hydrogen or methyl.

25. The method of claim 1 wherein R^6 is hydrogen.

26. The method of claim 1 wherein R^7 is hydrogen or methyl.

27. The method of claim 1 wherein R^7 is hydrogen.

28. The method of claim 1 wherein R^a and R^b are independently selected from the group consisting of hydrogen and C_{1-3}alkyl; or, when R^a and R^b are each other than hydrogen, R^a and R^b are optionally taken together with the nitrogen atom to which they are both attached to form a live to seven membered monocyclic ring.

29. The method of claim 1 wherein R^a and R^b are independently hydrogen or methyl.

30. The method of claim 1 wherein R^a and R^b are each hydrogen.

31. The method of claim 1 wherein said compounds are present in their RR, SS, RS, and SR configurations.

32. The method of claim 1 wherein said compounds are present in their S,S configuration.

33. The method of claim 1 wherein said compound is

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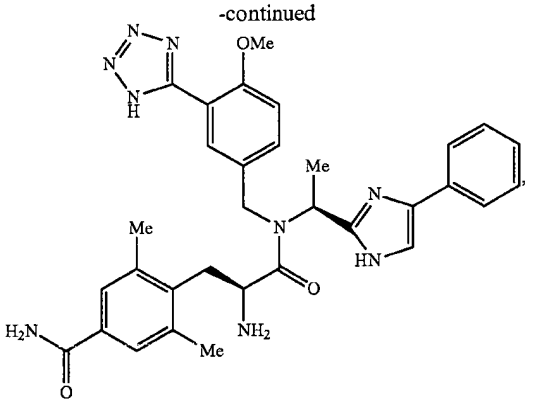

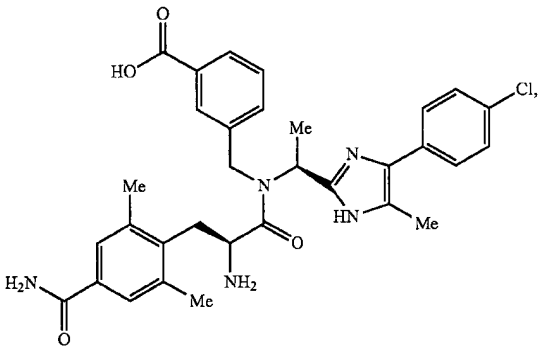

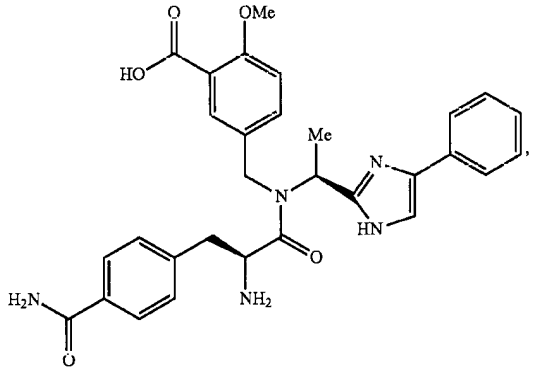

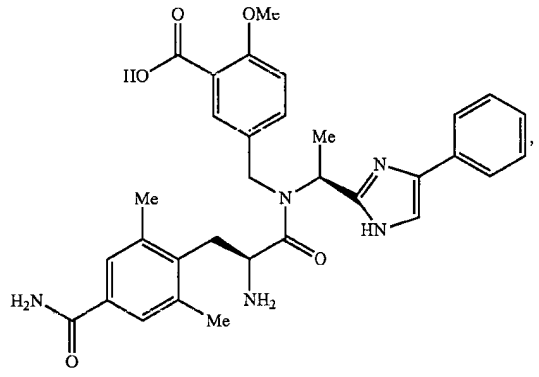

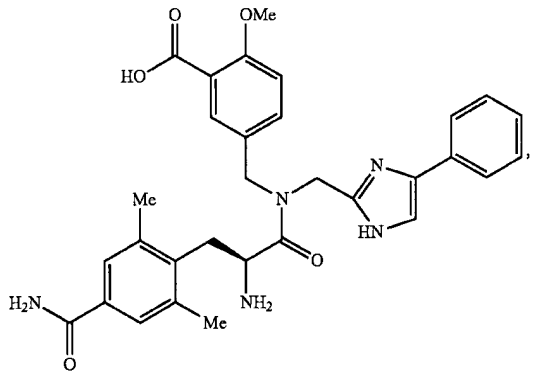

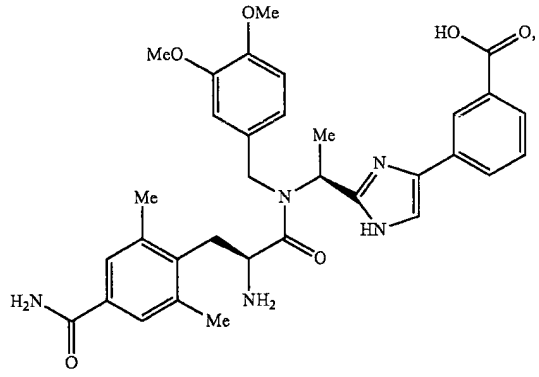

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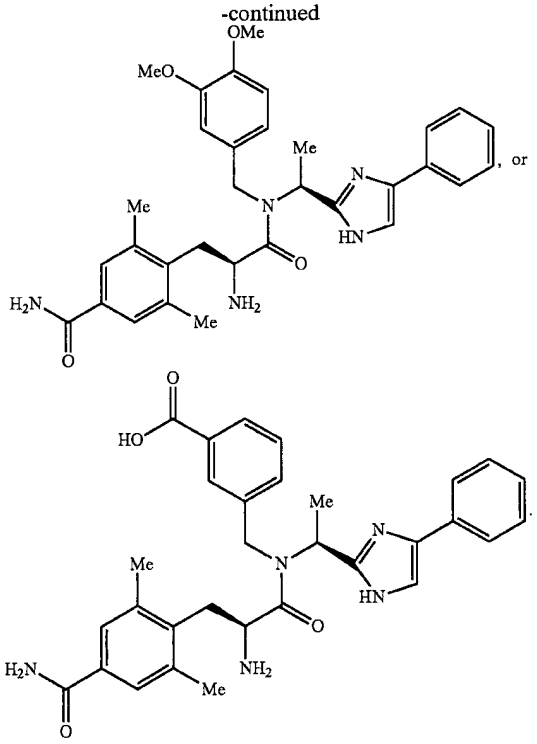

34. The method of claim 1 wherein said compound is the hydrochloride salt of 5-({[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid dihydrochloride.

35. The method of claim 1 wherein the compound is the hydrochloride salt of 5-({[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid.

36. The method of claim 1 wherein said pain is centrally mediated pain.

37. The method of claim 1 wherein said pain is peripherally mediated pain.

38. The method of claim 1 wherein said pain is structural or soft tissue injury related pain.

39. The method of claim 1 wherein said pain is related to inflammation.

40. The method of claim 1 wherein said pain is progressive disease related pain.

41. The method of claim 1 wherein said pain is neuropathic pain.

42. The method of claim 1 wherein said pain is acute pain.

43. The method of claim wherein said pain is or chronic pain.

44. The method of claim 1 wherein said gastrointestinal disorder is ulcerative colitis.

45. The method of claim 1 wherein said gastrointestinal disorder is Crohn's disease.

46. The method of claim 1 wherein said gastrointestinal disorder is diarrhea-predominant irritable bowel syndrome.

47. The method of claim 1 wherein said gastrointestinal disorder is alternating irritable bowel syndrome.

48. A method of claim 2 wherein:

R^1 is selected from the group consisting of C_{6-10}aryl(C_{1-4})alkyl, pyridinyl(C_{1-4})alkyl, and furanyl(C_{1-4})alkyl; wherein C_{6-10}aryl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-3}alkoxy; tetrazolyl; carboxy; C_{1-3}alkoxycarbonyl; aminocarbonyl; C_{1-4}alkylaminocarbonyl; C_{1-3}alkylaminocarbonyl; C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; cyano; halogen; trifluoromethoxy; C_{1-4}alkoxycathonyl; or carboxy; provided that no more than one R^{11} is C_{6-10}arylaminocarbonyl;

R^2 is hydrogen or C_{1-4}alkyl;

R^3 is one to two substituents independently selected from the group consisting of C_{1-3}alkyl, bromo, and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro, fluoro, carboxy, aminocarbonyl, and cyano;

R^4 is phenyl substituted with one to three substituents independently selected from the group consisting of (C_{1-3})alkyl, (C_{1-3})alkoxy, phenyl(C_{1-3})alkoxy, hydroxy, C_{1-6}alkylaminocarbonyl, and aminocarbonyl; provided that no more than one R^{41} substituent is aminocarbonyl, C_{1-6}alkylaminocarbonyl, hydroxy, or a phenyl-containing substituent;

R^5 is hydrogen;

R^a and R^b are independently hydrogen or methyl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

49. The method according to claim 2 wherein:

R^1 is selected from the group consisting of phenyl(C_{1-3})alkyl, pyridinyl(C_{1-3})alkyl, and furanyl(C_{1-3})alkyl; wherein phenyl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of is C_{1-3}alkoxy; tetrazolyl, C_{3-6}cycloalkylaminocarbonyl; hydroxy(C_{1-4})alkylaminocarbonyl; C_{6-10}arylaminocarbonyl wherein C_{6-10}aryl is optionally substituted with carboxy or C_{1-4}alkoxycarbonyl; morpholin-4-ylcarbonyl; chloro; fluoro; trifluoromethoxy; methoxycarbonyl; and carboxy; provided that no more than one R^{11} is C_{6-10}arylaminocarbonyl;

R^2 is hydrogen or methyl;

R^3 is one to two substituents independently selected from the group consisting of methyl and phenyl; wherein phenyl is optionally substituted with one to three substituents independently selected from the group consisting of chloro and carboxy;

R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two substituents independently selected from the group consisting of methyl, methoxy, and benzyloxy;

R^5 is hydrogen;

R^a and R^b are each hydrogen;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof.

50. The method according to claim 2 wherein R^1 is phenylmethyl, pyridinylmethyl, or furanylmethyl; wherein phenyl, pyridinyl, and furanyl are optionally substituted with one to three R^{11} substituents independently selected from is the group consisting of methoxy, tetrazolyl, cyclopropylaminocarbonyl, (2-hydroxyeth-1-yl)aminocarbonyl, phenylaminocarbonyl wherein phenyl is optionally substituted with carboxy, morpholin-4-ylcarbonyl, methoxycarbonyl, and carboxy; provided that no more than one R^{11} is phenylaminocarbonyl.

51. The method according to claim 2 wherein R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two methyl substituents.

52. The method according to claim 2 wherein R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and substituted at the 2- and 6-positions with methyl substituents.

53. The method of claim 2 wherein said pain is centrally mediated pain.

54. The method of claim 2 wherein said pain is peripherally mediated pain.

55. The method of claim 2 wherein said pain is structural or soft tissue injury related pain.

56. The method of claim 2 wherein said pain is related to inflammation.

57. The method of claim 2 wherein said pain is progressive disease related pain.

58. The method of claim 2 wherein said pain is neuropathic pain.

59. The method of claim 2 wherein said pain is acute pain.

60. The method of claim 2 wherein said pain is or chronic pain.

61. The method of claim 2 wherein said gastrointestinal disorder is ulcerative colitis.

62. The method of claim 2 wherein said gastrointestinal disorder is Crohn's disease.

63. The method of claim 2 wherein said gastrointestinal disorder is diarrhea-predominant irritable bowel syndrome.

64. The method of claim 2 wherein said gastrointestinal disorder is alternating irritable bowel syndrome.

65. A method for treating or pain or gastrointestinal disorder, wherein said pain is centrally mediated pain, peripherally mediated pain, structural or soft tissue injury related pain, pain related to inflammation, progressive disease related pain, neuropathic pain, acute pain, or chronic pain, and wherein said gastrointestinal disorder is ulcerative colitis, Crohn's disease, diarrhea-predominant irritable bowel syndrome, or alternating irritable bowel syndrome in a subject in need thereof comprising administering to the subject a therapeutically effective amount of 5-({[2-Amino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1H-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid or a pharmaceutically acceptable enantiomer, diastereomer, racemate, or salt thereof.

66. The method of claim 65 wherein the chronic pain is selected from the group consisting of neuropathic pain conditions, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, post-stroke pain syndromes and cluster or migraine headaches.

67. The method of claim 65 wherein said pain is centrally mediated pain.

68. The method of claim 65 wherein said pain is peripherally mediated pain.

69. The method of claim 65 wherein said pain is structural or soft tissue injury related pain.

70. The method of claim 65 wherein said pain is related to inflammation.

71. The method of claim 65 wherein said pain is progressive disease related pain.

72. The method of claim 65 wherein said pain is neuropathic pain.

73. The method of claim 65 wherein said pain is acute pain.

74. The method of claim 65 wherein said pain is or chronic pain.

75. The method of claim 65 wherein said gastrointestinal disorder is ulcerative colitis.

76. The method of claim 62 wherein said gastrointestinal disorder is Crohn's disease.

77. The method of claim 65 wherein said gastrointestinal disorder is diarrhea-predominant irritable bowel syndrome.

78. The method of claim 65 wherein said gastrointestinal disorder is alternating irritable bowel syndrome.

* * * * *

Exhibit 2

TOSARADocket No.: PRD2200USDIV1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. 8,344,011
Inventors:	Henry J. Breslin, Chaozhong Cai, Wei He, and Robert W. Kavash
Assignee:	Janssen Pharmaceutica, N.V.
Title:	Compounds as opioid receptor modulators
Issue Date:	January 1, 2013

CONSENT OF NDA HOLDER

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

Dear Madam:

Forest Tosara Limited ("Forest Tosara"), a corporation having offices and doing business at Unit 146, Baldoyle Industrial Estate, Grange Road, Dublin 13 Ireland, is the holder of new drug application (NDA) no. 206940 for VIBERZI™ (eluxadoline). Forest Tosara is a licensee of U.S. Patent No. 8,344,011 ("the '011 Patent"), which is assigned to Janssen Pharmaceutica, N.V. ("Janssen"), a corporation having offices and doing business at Turnhoutseweg 30, B-2340 Beerse, Belgium.

Forest Tosara hereby consents to and authorizes Janssen to act on its behalf with regard to any application submitted to the U.S. Patent and Trademark Office for extension of the term of the '011 Patent pursuant to 35 U.S.C. §156.

Dated: July 22, 2015

Respectfully submitted,

By: [signature]

Forest Tosara Limited

Name: Michael McDonald

Title: Director

Exhibit 3

PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

EPAS ID: PAT2813811

SUBMISSION TYPE:	NEW ASSIGNMENT
NATURE OF CONVEYANCE:	ASSIGNMENT

CONVEYING PARTY DATA

Name	Execution Date
HENRY J. BRESLIN	05/04/2005
CHAOZHONG CAI	05/05/2005
WEI HE	05/05/2005
ROBERT W. KAVASH	05/05/2005

RECEIVING PARTY DATA

Name:	JANSSEN PHARMACEUTICA, N.V.
Street Address:	TURNHOUTSEWEG 30
City:	BEERSE
State/Country:	BELGIUM
Postal Code:	B-2340

PROPERTY NUMBERS Total: 4

Property Type	Number
Patent Number:	7786158
Patent Number:	8344011
Patent Number:	8609709
Application Number:	14045008

CORRESPONDENCE DATA

Fax Number: (215)568-3439

Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent via US Mail.

Phone: 215-568-3100
Email: assignments@woodcock.com
Correspondent Name: BAKER & HOSTETLER LLP
Address Line 1: CIRA CENTRE - 12TH FLOOR
Address Line 2: 2929 ARCH STREET
Address Line 4: PHILADELPHIA, PENNSYLVANIA 19104

ATTORNEY DOCKET NUMBER:	103693.000153; 0408; 0495
NAME OF SUBMITTER:	JANIS CALVO
SIGNATURE:	/Janis Calvo/
DATE SIGNED:	04/15/2014

Total Attachments: 6
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DOCKET NO. PRD-2200USNP
Joint Inventors

A S S I G N M E N T

Serial No. 11/079,647
Filed March 14, 2005

WHEREAS, Henry J. Breslin, citizen of the United States of America, residing at 1974 Muhlenburg Drive, Lansdale, PA 19446, Chaozhong Cai, citizen of the People's Republic of China, residing at 129 Banbury Ave., N. Wales, PA 19454, Wei He, citizen of the United States of America, residing at 2002 Kestral Circle, Audubon, PA 19403, and Robert W. Kavash, citizen of the United States of America, residing at 148 N. Keswick Ave., Glenside, Pa 19038 respectively (hereinafter called "Assignors"), have made certain new and useful inventions or discoveries relating to

NOVEL COMPOUNDS AS OPIOID RECEPTOR MODULATORS

filed an application for Letters Patent of the United States; and

WHEREAS, Janssen Pharmaceutica, N.V., a corporation of the State of Belgium, (hereinafter called "Assignee"), is desirous of acquiring Assignors' entire right, title, and interest therein:

NOW, THEREFORE, BE IT KNOWN that for and in consideration of the sum of One Dollar and other valuable considerations, the receipt of which is hereby acknowledged, Assignors have sold, assigned, and transferred, and do hereby sell, assign and transfer unto said Assignee their entire right, title and interest in and to all said inventions and discoveries disclosed in said application whose identification above by serial number and filing date, when available is hereby authorized, and in and to said application, all substitutions, divisions, and continuations thereof, and in and to all Letters Patent, United States and foreign, that may be granted for said inventions and discoveries, and in and to all extensions, renewals, and reissues thereof, the same to be held and enjoyed by said Assignee, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by Assignors if this Assignment and sale had not been made;

And Assignors hereby authorize and request the Commissioner of Patents of the United States to issue said Letters Patent in accordance with this Assignment;

And for the consideration aforesaid, Assignors covenant and agree with said Assignee that he has a full and unencumbered title to the inventions and discoveries above described and hereby assigned, which title they warrant unto said Assignee, its successors and assigns;

And for the consideration aforesaid, Assignors further covenant and agree that they will, whenever requested, but without cost to them promptly communicate to said Assignee or its representatives any facts known to them relating to said inventions and discoveries, testify in any interference or legal proceedings involving said inventions and discoveries, and execute any additional papers that may be necessary to enable said Assignee or its representatives, successors, nominees, or assigns to secure full and complete protection for the said inventions and discoveries or that may be necessary to vest in said Assignee the complete title to the said inventions and discoveries and patents hereby conveyed and to enable it to record said title.

IN TESTIMONY WHEREOF, Assignor has hereunto set his hand and seal this 4th day of May, 2005

Henry J. Breslin (L.S.)

STATE OF Pennsylvania)
) ss.
COUNTY OF Montgomery)

BE IT REMEMBERED, That on this 4th day of May, 2005, before me, a Notary Public, personally appeared Henry J. Breslin who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him the content thereof, he did acknowledge that he signed, sealed, and delivered the same as his voluntary act and deed for the uses and purposes therein expressed.

Notary Public

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Christine M. Razler, Notary Public
Lower Gwynedd Twp., Montgomery County
My Commission Expires Nov. 19, 2007
Member, Pennsylvania Association Of Notaries

IN TESTIMONY WHEREOF, Assignor has hereunto set his/her hand and seal this 5th day of May, 2005

Chaozhong Cai (L.S.)

Chaozhong Cai

STATE OF Pennsylvania)
) ss.
COUNTY OF Montgomery)

BE IT REMEMBERED, That on this 5th day of May, 2005, before me, a Notary Public, personally appeared Chaozhong Cai who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him/her the contents thereof, he/she did acknowledge that he/she signed, sealed, and delivered the same as his/her voluntary act and deed for the uses and purposes therein expressed.

Christine M Razler

Notary Public

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Christine M. Razler, Notary Public
Lower Gwynedd Twp., Montgomery County
My Commission Expires Nov. 19, 2007
Member Pennsylvania Association Of Notaries

IN TESTIMONY WHEREOF, Assignor has hereunto set his/her hand and seal this 5th day of MAY, 2005

Wei He (L.S.)

STATE OF Pennsylvania)
) ss.
COUNTY OF Montgomery)

BE IT REMEMBERED, That on this 5th day of May, 2005, before me, a Notary Public, personally appeared Wei He who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him/her the content thereof, he/she did acknowledge that he/she signed, sealed, and delivered the same as his/her voluntary act and deed for the uses and purposes therein expressed.

Christine M Razler
Notary Public

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Christine M. Razler, Notary Public
Lower Gwynedd Twp., Montgomery County
My Commission Expires Nov. 19, 2007
Member, Pennsylvania Association Of Notaries

IN TESTIMONY WHEREOF, Assignor has hereunto set his hand and seal this 5th day of May, 2005

Robert W. Kavash (L.S.)
Robert W. Kavash

STATE OF Pennsylvania)
COUNTY OF Montgomery) ss.

BE IT REMEMBERED, That on this 5th day of May, 2005, before me, a Notary Public, personally appeared Robert W. Kavash who I am satisfied is the person named in and who executed the foregoing instrument in my presence, and I having first made known to him the content thereof, he did acknowledge that he signed, sealed, and delivered the same as his voluntary act and deed for the uses and purposes therein expressed.

Christine M Razler
Notary Public

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Christine M. Razler, Notary Public
Lower Gwynedd Twp., Montgomery Co
My Commission Expires Nov. 19, 200
Member, Pennsylvania Association Of Nota

COMMONWEALTH OF PENNSYLVANIA
Notarial Seal
Christine M. Razler, Notary Public
Lower Gwynedd Twp., Montgomery County
My Commission Expires Nov. 19, 2007
Member, Pennsylvania Association Of Notaries

Exhibit 4

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206940

NDA APPROVAL

Furiex Pharmaceuticals, Inc.
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
3900 Paramount Parkway Suite 150
Morrisville, North Carolina 27560

Dear Ms. Usher:

Please refer to your New Drug Application (NDA) dated June 26, 2014, received June 27, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Viberzi (eluxadoline) Tablets, 75 mg and 100 mg.

We acknowledge receipt of your amendments dated July 18, 2014, August 12, 2014, August 15, 2014, August 19, 2014, August 22, 2014, August 29, 2014, September 22, 2014, October 9, 2014, October 17, 2014, October 23, 2014, December 2, 2014, December 3, 2014, December 9, 2014, December 12, 2014, December 23, 2014, January 8, 2015, January 9, 2015, January 12, 2015, January 30, 2015, February 11, 2015, February 12, 2015, February 18, 2015, February 20, 2015, February 24, 2015, February 27, 2015, March 11, 2015, March 17, 2015, May 4, 2015, May 7, 2015, May 8, 2015, May 13, 2015, May 18, 2015, May 21, 2015, May 22, 2015, and May 26, 2015.

This new drug application provides for the use of Viberzi (eluxadoline) Tablets, 75 mg and 100 mg for adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

CONTROLLED SUBSTANCE SCHEDULING

The final scheduling of this product under the Controlled Substances Act is currently proceeding, but not yet complete as of the date of this letter. We remind you of your signed agreement on Form 356h dated June 26, 2014 and received June 27, 2014 and your agreement on May 20, 2015 not to market this drug until the Drug Enforcement Administration has made a final scheduling decision. We further note that, when the scheduling is finalized, you will need to make appropriate revisions to the package insert, the patient package insert and the carton and immediate-container labels through supplementation of your NDA. This would include the statements detailing the scheduling of Viberzi in the labeling, as required under 21 CFR 201.57(a)(2) and (c)(10)(i).

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

WAIVER OF PREGNANCY, LABOR AND DELIVERY, AND NURSING MOTHERS SUBSECTIONS

We are waiving the current requirements of 21 CFR 201.56(d)(1) and 201.57(c)(9)(i) through (iii), regarding the content and format of labeling for subsections 8.1 Pregnancy, 8.2 Labor and Delivery, and 8.3 Nursing Mothers of prescribing information. Your approved labeling for subsections 8.1, 8.2, and 8.3 reflects the content and format requirements of the Pregnancy and Lactation Labeling Rule (79 FR 72063, December 4, 2014) which implements on June 30, 2015.

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 the Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositorics.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels 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 *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 206940.**" 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 Viberzi was not referred to an FDA advisory committee because the clinical trial design is acceptable, outside expertise was not necessary, and there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for ages 0 through 5 years because necessary studies are impossible or highly impracticable. This is based on the lack of prevalence data on IBS-D in this age group.

We are deferring submission of your pediatric studies for ages 6 through 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

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

2901-1 Conduct a dose ranging study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D). The pharmacokinetics of eluxadoline in these pediatric patients should also be characterized.

Final Protocol Submission:	06/01/2016
Study Completion:	10/15/2019
Final Report Submission:	01/15/2020

2901-2 Conduct a randomized, double-blind study to determine the safety and effectiveness of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D).

Final Protocol Submission:	03/31/2020
Study Completion:	03/15/2026
Final Report Submission:	06/15/2026

2901-3 Conduct an open-label extension safety study of eluxadoline in pediatric patients 6 through 17 years with diarrhea-predominant irritable bowel syndrome (IBS-D) who participated in the dose ranging (# 2901-1) or efficacy (# 2901-2) studies.

Final Protocol Submission:	03/31/2020
Study Completion:	03/15/2027
Final Report Submission:	06/15/2027

Submit the protocols to your IND 079214, with a cross-reference letter to this NDA.

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

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 identify an unexpected serious risk of euphoria and other central nervous system (CNS) adverse effects based on increased drug concentrations in patients with renal insufficiency.

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 this serious risk.

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

2901-4 A dedicated clinical pharmacology trial to evaluate the impact of renal impairment on eluxadoline pharmacokinetics and the risk for euphoria and other central nervous system (CNS) adverse effects.

The timetable you submitted on May 7, 2015, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	01/01/2016
Trial Completion:	12/31/2017
Final Report Submission:	06/30/2018

Submit the protocol to your IND 079214, with a cross-reference letter to this NDA. Submit the final report 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:

2901-5 Conduct an *in vitro* study to determine the specific isozymes involved in the metabolism of eluxadoline.

The timetable you submitted on May 7, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/01/2016
Study Completion:	12/31/2016
Final Report Submission:	03/31/2017

2901-6 Conduct an *in vitro* study to assess the time-dependent inhibition of CYP3A4 by eluxadoline.

The timetable you submitted on May 7, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/01/2016
Study Completion:	12/31/2016
Final Report Submission:	03/31/2017

2901-7 Conduct an *in vitro* study to estimate the IC_{50} (or K_i) value of eluxadoline with respect to P-gp and predict the *in vivo* relevance of this interaction.

The timetable you submitted on May 7, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/01/2016
Study Completion:	12/31/2016
Final Report Submission:	03/31/2017

2901-8 Conduct an *in vitro* study to evaluate the potential of eluxadoline to inhibit CYP2C8 and induce CYP2B6.

The timetable you submitted on May 7, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/01/2016
Study Completion:	12/31/2016
Final Report Submission:	03/31/2017

2901-9 Conduct a study of the product dissolution and acceptance criterion to assess post-approval product quality using the following:

- Re-evaluate the dissolution acceptance criterion based on the dissolution data collected from at least 10 batches of commercial drug products (5 batches of 75 mg and 5 batches of 100 mg), manufactured over a maximum period of 1 year post-launch.

- Add a 15-minute time-point to the dissolution test at time of product release and in the stability protocol where profiles will be followed at 10, 15, 20, 30, 45, and 60 minutes.

- Assess the dissolution criterion of Q= (b) (4) % at 10, 15, or 20-minute time points and submit the newly proposed dissolution criterion with supportive dissolution profile data to the Agency for review.

The timetable you submitted on May 14, 2015, states that you will conduct this study according to the following schedule:

Completion of dissolution data assessment:	Launch date + 12 months
Submission of dissolution data assessment:	Launch date + 14 months

Submit clinical protocols to your IND 079214 for this product. Submit nonclinical and 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 study 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

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

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

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

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

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

POST APPROVAL FEEDBACK MEETING

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

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 Jennifer Sarchet, Regulatory Project Manager, at 240-402-4275.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

JULIE G BEITZ
05/27/2015

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VIBERZI (eluxadoline) tablets, for oral use, C-X
Initial U.S. Approval: 2015

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

VIBERZI is a mu-opioid receptor agonist, indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D). (1)

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

- The recommended dosage in adults is 100 mg twice daily taken with food. (2)
- The recommended dosage is 75 mg twice daily taken with food in patients who:
  - do not have a gallbladder (2, 5.1)
  - are unable to tolerate the 100 mg dose (2, 6.1)
  - are receiving concomitant OATP1B1 inhibitors (2, 7)
  - have mild or moderate hepatic impairment (2, 8.6)
- Discontinue VIBERZI in patients who develop severe constipation for more than 4 days (2)
- If a dose is missed, take the next dose at the regular time; do not take 2 doses at once (2)

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

75 mg and 100 mg tablets (3)

----------CONTRAINDICATIONS----------

Patients with:

- known or suspected biliary duct obstruction, or sphincter of Oddi disease or dysfunction (4)
- alcoholism, alcohol abuse, alcohol addiction, or drink more than 3 alcoholic beverages/day (4)
- a history of pancreatitis; structural diseases of the pancreas, including known or suspected pancreatic duct obstruction (4)
- severe hepatic impairment (Child-Pugh Class C) (4, 8.6)
- severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction (4)

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

- Sphincter of Oddi Spasm and Pancreatitis: Monitor patients without a gallbladder for new or worsening abdominal pain, with or without nausea and vomiting, or acute biliary pain with liver or pancreatic enzyme elevations; discontinue VIBERZI and seek medical attention if symptoms develop. (5.1, 5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (>5%) are constipation, nausea and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Forest Pharmaceuticals, Inc., at 1- 800- 678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

See full prescribing information. (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: May 2015

FULL PRESCRIBING INFORMATION CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VIBERZI is indicated in adults for the treatment of irritable bowel syndrome with diarrhea (IBS-D).

2 DOSAGE AND ADMINISTRATION

The recommended dosage of VIBERZI is 100 mg taken orally twice daily with food.

The recommended dosage of VIBERZI is 75 mg taken orally twice daily with food in patients who:

- do not have a gallbladder *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.
- are unable to tolerate the 100 mg dose of VIBERZI *[see Adverse Reactions (6.1)]*.
- are receiving concomitant OATP1B1 inhibitors *[see Drug Interactions (7)]*.
- have mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment *[see Use in Specific Population (8.6), Clinical Pharmacology (12.3)]*.

Discontinue VIBERZI in patients who develop severe constipation for more than 4 days.

Instruct patients if they miss a dose, take the next dose at the regular time and not to take 2 doses at the same time to make up for a missed dose.

3 DOSAGE FORMS AND STRENGTHS

- 75 mg tablets: capsule-shaped tablets are coated in pale-yellow to light tan color debossed with "FX75" on one side. Each tablet contains 75 mg eluxadoline.
- 100 mg tablets: capsule-shaped tablets are coated in pink-orange to peach color debossed with "FX100" on one side. Each tablet contains 100 mg eluxadoline.

4 CONTRAINDICATIONS

VIBERZI is contraindicated in patients with:

- Known or suspected biliary duct obstruction; or sphincter of Oddi disease or dysfunction. These patients are at increased risk for sphincter of Oddi spasm *[see Warnings and Precautions (5.1)]*.

- Alcoholism, alcohol abuse or alcohol addiction, or in patients who drink more than 3 alcoholic beverages per day. These patients are at increased risk for acute pancreatitis *[see Warnings and Precautions (5.2)]*.

- A history of pancreatitis; or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction. These patients are at increased risk for acute pancreatitis *[see Warnings and Precautions (5.2)]*.

- Severe hepatic impairment (Child-Pugh Class C). These patients are at risk for significantly increased plasma concentrations of eluxadoline *[see Use in Specific Populations (8.6)]*

- A history of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction. These patients may be at risk for severe complications of bowel obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Sphincter of Oddi Spasm

Given the mu opioid receptor agonism of VIBERZI, there is a potential for increased risk of sphincter of Oddi spasm, resulting in pancreatitis or hepatic enzyme elevation associated with acute abdominal pain (e.g., biliary-type pain) with VIBERZI.

In clinical trials, sphincter of Oddi spasm occurred in less than 1% of patients receiving VIBERZI. The majority of these patients presented within the first week of treatment and the event resolved on discontinuation of VIBERZI. Patients without a gallbladder are at increased risk *[see Adverse Reactions (6.1)]*.

Consider alternative therapies before using VIBERZI in patients without a gallbladder and evaluate the benefits and risks of VIBERZI in these patients in the context of their symptom severity. The recommended dosage of VIBERZI is 75 mg twice daily in patients without a gallbladder *[see Dosage and Administration (2)]*. If VIBERZI is used in such a patient, inform them that they may be at increased risk for adverse reactions and monitor them for symptoms of sphincter of Oddi spasm, such as elevated liver transaminases associated with abdominal pain or pancreatitis, especially during the first few weeks of treatment.

Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms suggestive of sphincter of Oddi spasm such as acute worsening of abdominal pain, (e.g. acute epigastric or biliary [i.e., right upper quadrant] pain), that may radiate to the back or shoulder with or without nausea and vomiting, associated with elevations of pancreatic enzymes or liver transaminases. Do not restart VIBERZI in patients who developed biliary duct obstruction or sphincter of Oddi spasm while taking VIBERZI *[see Contraindications (4)]*.

5.2 Pancreatitis

There is a potential for increased risk of pancreatitis, not associated with sphincter of Oddi spasm, when taking VIBERZI. Additional cases of pancreatitis, not associated with sphincter of Oddi spasm, were reported in less than 1% of patients receiving VIBERZI in clinical trials. The majority were associated with excessive alcohol intake. All pancreatic events, whether or not associated with sphincter of Oddi spasm, resolved upon discontinuation of VIBERZI; patients did not have organ failure or local or systemic complications *[see Adverse Reactions (6.1)]*.

Instruct patients to avoid chronic or acute excessive alcohol use while taking VIBERZI. Monitor for new or worsening abdominal pain that may radiate to the back or shoulder, with or without nausea and vomiting. Instruct patients to stop VIBERZI and seek medical attention if they experience symptoms suggestive of pancreatitis such as acute abdominal or epigastric pain radiating to the back associated with elevations of pancreatic enzymes *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following adverse reactions described below and elsewhere in the labeling include:

- Sphincter of Oddi Spasm *[see Warnings and Precautions (5.1)]*
- Pancreatitis *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates 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.

Over 1700 patients with IBS-D have been treated with 75 or 100 mg of VIBERZI twice daily in controlled trials. Exposures from placebo-controlled clinical trials in adult patients with IBS-D included 1391 exposed for 3 months, 1001 exposed for 6 months and 488 exposed for one year.

Demographic characteristics were comparable between the treatment groups *[see Clinical Studies (14)]*. Data described below represent pooled data compared to placebo across the randomized trials.

Sphincter of Oddi Spasm
In clinical trials, sphincter of Oddi spasm occurred in 0.2% (2/807) of patients receiving 75 mg and 0.8% (8/1032) of patients receiving 100 mg VIBERZI twice daily.

- Among patients receiving 75 mg, 1/807 (0.1%) patient experienced a sphincter of Oddi spasm presenting with abdominal pain but with lipase elevation less than 3 times the

upper limit of normal (ULN) and 1/ 807 (0.1%) patient experienced a sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain

- Among patients receiving 100 mg, 1/1032 (0.1%) patient experienced a sphincter of Oddi spasm manifested as pancreatitis and 7/1032 (0.7%) patients experienced sphincter of Oddi spasm manifested as elevated hepatic enzymes associated with abdominal pain

In patients without a gallbladder, 2/165 (1.2%) and 8/184 (4.3%) of patients receiving 75 mg and 100 mg, respectively, experienced a sphincter of Oddi spasm vs 0/1317 (0%) in patients with a gallbladder who had received either 75 mg or 100 mg treatment.

Of those patients who experienced a sphincter of Oddi spasm, 80% (8/10) reported their first onset of symptoms within the first week of treatment. The case of sphincter of Oddi spasm-induced pancreatitis occurred within minutes of taking the first dose of VIBERZI. No cases of sphincter of Oddi spasm occurred greater than 1 month after treatment onset. All events resolved upon discontinuation of VIBERZI, with symptoms typically improved by the following day.

Pancreatitis
Additional cases of pancreatitis, not associated with sphincter of Oddi spasm, were reported in 2/807 (0.2%) of patients receiving 75 mg and 3/1032 (0.3%) of patients receiving 100 mg VIBERZI twice daily in clinical trials. Of these 5 cases, 3 were associated with excessive alcohol intake, one was associated with biliary sludge, and in one case the patient discontinued VIBERZI 2 weeks prior to the onset of symptoms. All pancreatic events resolved with lipase normalization upon discontinuation of VIBERZI, with 80% (4/5) resolving within 1 week of treatment discontinuation. The case of sphincter of Oddi spasm-induced pancreatitis resolved within 24 hours of discontinuation.

Common Adverse Reactions
Table 1 provides the incidence of common adverse reactions reported in > 2% of IBS-D patients in either VIBERZI treatment group and at an incidence greater than in the placebo group.

Table 1: Common* Adverse Reactions in the Placebo-Controlled Studies in IBS-D Patients

Adverse Reactions	VIBERZI 100 mg twice daily (N= 1032) %	VIBERZI 75 mg twice daily (N=807) %	Placebo (N=975) %
Constipation	8	7	3
Nausea	7	8	5
Abdominal Pain**	7	6	4
Upper Respiratory Tract Infection	5	3	4
Vomiting	4	4	1
Nasopharyngitis	3	4	3
Abdominal Distention	3	3	2
Bronchitis	3	3	2
Dizziness	3	3	2
Flatulence	3	3	2
Rash***	3	3	2
Increased ALT	3	2	1
Fatigue	2	3	2
Viral gastroenteritis	1	3	2

* Reported in > 2% of VIBERZI-treated patients at either dose and at an incidence greater than in placebo-treated patients

** "Abdominal Pain" term includes: abdominal pain, abdominal pain lower, and abdominal pain upper

*** "Rash" term includes: dermatitis, dermatitis allergic, rash, rash erythematous, rash generalized, rash maculo-papular, rash papular, rash pruritic, urticaria, and idiopathic urticaria

Constipation was the most commonly reported adverse reaction in VIBERZI-treated patients in these trials. Approximately 50% of constipation events occurred within the first 2 weeks of treatment while the majority occurred within the first 3 months of therapy. Rates of severe constipation were less than 1% in patients receiving 75 mg and 100 mg VIBERZI. Similar rates of constipation occurred between the active and placebo arms beyond 3 months of treatment.

Adverse Reactions Leading to Discontinuation

Eight percent of patients treated with 75 mg, 8% of patients treated with 100 mg VIBERZI and 4% of patients treated with placebo discontinued prematurely due to adverse reactions. In the VIBERZI treatment groups, the most common reasons for discontinuation due to adverse reactions were constipation (1% for 75 mg and 2% for 100 mg) and abdominal pain (1% for both 75 mg and 100 mg). In comparison, less than 1% of patients in the placebo group withdrew due to constipation or abdominal pain.

Less Common Adverse Reactions

Adverse reactions that were reported in ≤ 2% of VIBERZI-treated patients are listed below by body system.

Gastrointestinal: gastroesophageal reflux disease

General Disorders and administration site conditions: feeling drunk
Investigations: increased AST
Nervous system: sedation, somnolence
Psychiatric disorders: euphoric mood
Respiratory: asthma, bronchospasm, respiratory failure, wheezing

7 DRUG INTERACTIONS

The metabolism of eluxadoline by CYP pathways has not been clearly established. In addition, the potential of eluxadoline to inhibit CYP3A4 in the gut has not been established.

Tables 2 and **3** include drugs which demonstrated a clinically important drug interaction with VIBERZI or which potentially may result in clinically relevant interactions.

Table 2: Established and Other Potentially Clinically Relevant Interactions Affecting VIBERZI

OATP1B1 Inhibitors	
Clinical Impact:	Increased exposure to eluxadoline when coadministered with cyclosporine *[see Clinical Pharmacology (12.3)]*
Intervention:	Administer VIBERZI at a dose of 75 mg twice daily *[see Dosage and Administration (2)]* and monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions (6.1)]*.
Examples:	cyclosporine, gemfibrozil, antiretrovirals (atazanavir, lopinavir, ritonavir, saquinavir, tipranavir), rifampin, eltrombopag
Strong CYP Inhibitors*	
Clinical Impact:	Potential for increased exposure to eluxadoline *[see Clinical Pharmacology (12.3)]*
Intervention:	Monitor patients for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions (6.1)]*.
Examples:	ciprofloxacin, (CYP1A2), gemfibrozil (CYP2C8), fluconazole, (CYP2C19), clarithromycin (CYP3A4), paroxetine and bupropion, (CYP2D6)
Drugs that Cause Constipation	
Clinical Impact:	Increased risk for constipation related adverse reactions and potential for constipation related serious adverse reactions
Intervention:	Avoid use with other drugs that may cause constipation (see below); loperamide may be used occasionally for acute management of severe diarrhea but avoid chronic use. Discontinue loperamide immediately if constipation occurs.
Examples:	alosetron, anticholinergics, opioids

*As a precautionary measure due to incomplete information on the metabolism of eluxadoline

Table 3: Established and Other Potentially Clinically Relevant Interactions Affecting Drugs Co-Administered with VIBERZI

OATP1B1 and BCRP Substrate	
Clinical Impact:	VIBERZI may increase the exposure of co-administered OATP1B1 and BCRP substrates. Increased exposure to rosuvastatin when co-administered with VIBERZI with a potential for increased risk of myopathy/rhabdomyolysis *[see Clinical Pharmacology (12.3)]*
Intervention:	Use the lowest effective dose of rosuvastatin (see prescribing information of rosuvastatin for additional information on recommended dosing).
CYP3A Substrates with Narrow Therapeutic Index	
Clinical Impact:	Potential for increased exposure of co-administered drug *[see Clinical Pharmacology (12.3)]*
Intervention:	Monitor drug concentrations or other pharmacodynamic markers of drug effect when concomitant use with eluxadoline is initiated or discontinued.
Examples:	alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies with VIBERZI in pregnant women that inform any drug-associated risks. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies. In animal reproduction studies, oral and subcutaneous administration of eluxadoline to rats and rabbits during organogenesis at doses approximately 51 and 115 times the human exposure after a single oral dose of 100 mg, respectively, demonstrated no teratogenic effects. In a pre- and postnatal development study in rats, no adverse effects were observed in offspring with oral administration of eluxadoline at doses approximately 10 times the human exposure *[see Data]*.

Data

Animal Data

Eluxadoline administered as combined oral (1000 mg/kg/day) and subcutaneous (5 mg/kg/day) doses during the period of organogenesis to rats and rabbits (exposures about 51 and 115 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) did not cause any adverse effects on embryofetal development. A pre- and postnatal development study in rats showed no evidence of any adverse effect on pre- and postnatal development at oral doses of eluxadoline up to 1000 mg/kg/day (with exposures about 10 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). In the same study, eluxadoline was detected in the

milk of lactating rats administered oral doses of 100, 300 and 1000 mg/kg/day (with exposures about 1.8, 3 and 10 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). Milk samples were collected from six lactating females per group on lactation day 12. Mean concentrations of eluxadoline in the milk of lactating rats on lactation day 12 were 2.78, 5.49 and 44.02 ng/mL at 100, 300 and 1000 mg/kg/day, respectively.

8.2 Lactation

Risk Summary

No data are available regarding the presence of eluxadoline in human milk, the effects of eluxadoline on the breastfed infant, or the effects of eluxadoline on milk production. However, eluxadoline is present in rat milk *[see Use in Specific Populations (8.1)]*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIBERZI and any potential adverse effects on the breastfed infant from VIBERZI or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Juvenile Toxicology Data

Eluxadoline was orally administered to juvenile rats at 500, 750, and 1500 mg/kg/day (about 16, 54 and 30 times, respectively, the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) for 4 weeks. There were no adverse physiologic effects related to eluxadoline. Based on these results, the NOAEL for male and female juvenile rats was 1500 mg/kg/day (about 30 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg).

8.5 Geriatric Use

Of 1795 IBS-D patients in clinical trials of VIBERZI who received 75 mg or 100 mg twice daily, 139 (7.7%) were at least 65 years of age, while 15 (0.8%) were at least 75 years old. No overall differences in effectiveness were observed between these patients and younger patients. There were no overall differences in the types of adverse reactions observed between elderly and younger patients; however, a higher proportion of elderly patients than younger patients experienced adverse reactions (66% vs 59%), serious adverse reactions (9% vs 4%), and gastrointestinal adverse reactions (39% vs 28%).

8.6 Hepatic Impairment

Plasma concentrations of eluxadoline increase in patients with hepatic impairment *[see Clinical Pharmacology (12.3)]*.

VIBERZI is contraindicated in patients with severe hepatic impairment (Child-Pugh Class C) as plasma concentrations of eluxadoline increase significantly (16-fold) and there is no information to support the safety of VIBERZI in these patients.

In patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, plasma concentrations of eluxadoline increase to a lesser extent (4- and 6-fold, respectively). Administer VIBERZI at a reduced dose of 75 mg twice daily to these patients *[see Dosage and Administration (2)]*. Monitor patients with any degree of hepatic impairment for impaired mental or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery and for other eluxadoline-related adverse reactions *[see Adverse Reactions (6.1)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Pending

9.2 Abuse

In a drug discrimination study in monkeys, intravenous administration of eluxadoline hydrochloride produced full generalization to the morphine cue. In a self-administration study in monkeys, eluxadoline hydrochloride was self-administered to a degree that was less than that of heroin but greater than that of saline.

Adverse reactions of euphoria and feeling drunk were reported in clinical trials of IBS-D evaluating 75 mg and 100 mg doses of VIBERZI. The rate of euphoria was 0% for 75 mg and 0.2% (2/1032) for 100 mg and the rate of feeling drunk was 0.1% (1/807) for 75 mg and 0.1% (1/1032) for 100 mg.

In contrast, in two human abuse potential studies conducted in recreational opioid-experienced individuals, supratherapeutic oral doses of VIBERZI (300 mg and/or 1000 mg) and intranasal doses of VIBERZI (100 mg and/or 200 mg) produced the adverse reaction of euphoria (at a rate ranging from 14% to 28%) that was greater than that of placebo (0% to 5%) but less than that of oxycodone (44% to 76%). In the two human abuse potential studies, supratherapeutic oral and intranasal doses of VIBERZI produced small but significant increases on positive subjective measures such as Drug Liking and High compared to placebo. Supratherapeutic oral and intranasal doses of VIBERZI also produced small but significant increases on negative subjective measures such as Drug Disliking and Dysphoria compared to placebo. In the same studies, oxycodone (30 mg and 60 mg oral, and 15 and 30 mg intranasal) produced significantly greater responses on positive and negative subjective measures than those produced by eluxadoline and placebo.

9.3 Dependence

In studies with monkeys and rats in which eluxadoline and eluxadoline hydrochloride were chronically administered, discontinuation of the drug did not lead to behavioral signs of withdrawal, a measure of physical dependence. However, the ability of eluxadoline hydrochloride in monkeys to induce self-administration suggests that the drug is sufficiently rewarding to produce reinforcement. In two human abuse potential studies with VIBERZI conducted in recreational opioid-experienced individuals, euphoria was reported at a rate of 14% to 28%. These data suggest that eluxadoline may produce psychological dependence.

10 OVERDOSAGE

No reports of overdosage with VIBERZI have been reported.

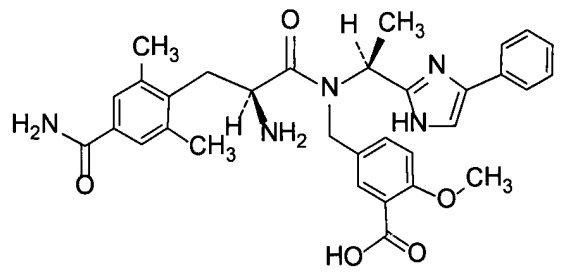
In the event of acute overdose, the stomach should be emptied and adequate hydration maintained. The patient should be carefully observed and given standard supportive treatment as required. Given eluxadoline's action at opioid receptors, administration of a narcotic mu-opioid antagonist, such as naloxone, should be considered. Considering the short half-life of naloxone, repeated administration may be necessary. In the event of naloxone administration, subjects should be monitored closely for the return of overdose symptoms, which may indicate need for repeated naloxone injection.

11 DESCRIPTION

The active ingredient in VIBERZI is eluxadoline, a mu-opioid receptor agonist.

The full chemical name is 5-[[[(2S)-2-amino-3-[4-(aminocarbonyl)-2,6-dimethylphenyl]-1-oxopropyl][(1S)-1-(4-phenyl-1H-imidazol-2-yl)ethyl]amino]methyl]-2-methoxybenzoic acid.

Eluxadoline has a molecular weight of 569.65 and a molecular formula of $C_{32}H_{35}N_5O_5$. The chemical structure of eluxadoline is:



VIBERZI is available as 75 mg and 100 mg tablets for oral administration. In addition to the active ingredient, eluxadoline, each tablet contains the following inactive ingredients: silicified

microcrystalline cellulose, colloidal silica, crospovidone, mannitol, magnesium stearate, and Opadry II (partially hydrolyzed polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Eluxadoline is a mu-opioid receptor agonist; eluxadoline is also a delta opioid receptor antagonist and a kappa opioid receptor agonist. The binding affinities (Ki) of eluxadoline for the human mu and delta opioid receptors are 1.8 nM and 430 nM, respectively. The binding affinity (Ki) of eluxadoline for the human kappa opioid receptor has not been determined; however, the Ki for guinea pig cerebellum kappa opioid receptor is 55 nM. In animals, eluxadoline interacts with opioid receptors in the gut.

12.2 Pharmacodynamics

Cardiac Electrophysiology
At a dose 10 times the maximum recommended dose (100 mg), VIBERZI does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Following oral administration of 100 mg VIBERZI in healthy subjects, the C_{max} of eluxadoline was approximately 2 to 4 ng/mL and AUC was 12 to 22 ng.h/mL. Eluxadoline has approximately linear pharmacokinetics with no accumulation upon repeated twice daily dosing. The variability of eluxadoline pharmacokinetic parameters ranges from 51% to 98%.

Absorption

Absolute bioavailability of eluxadoline has not been determined. The median T_{max} value was 1.5 hours (range: 1 to 8 hours) under fed conditions and 2 hours (range: 0.5 to 6 hours) under fasting conditions.

The administration of VIBERZI with a high fat meal that contained approximately 800 to 1000 total calories, with 50% of calories being derived from fat content decreased the C_{max} of eluxadoline by 50% and AUC by 60%.

Distribution

Plasma protein binding of eluxadoline was 81%.

Elimination

The mean plasma elimination half-life of eluxadoline ranged from 3.7 hours to 6 hours.

Metabolism

Metabolism of eluxadoline is not clearly established *[see Drug Interactions (7)]*. There is evidence that glucuronidation can occur to form an acyl glucuronide metabolite.

Excretion

Following a single oral dose of 300 mg [^{14}C] eluxadoline in healthy male subjects, 82.2% of the total radioactivity was recovered in feces within 336 hours and less than 1% was recovered in urine within 192 hours.

Specific Populations

Hepatic Impairment

Following a single oral 100–mg dose in subjects with varying degrees of liver impairment and healthy subjects, mean eluxadoline plasma exposure was 6-fold, 4-fold, and 16-fold higher in mild, moderate, and severe hepatically impaired subjects (Child Pugh Class A, B, C), respectively, compared to the subjects with normal liver function *[see Dosage and Administration (2), Contraindications (4), Use in Specific Populations (8.6)]*.

Drug Interactions

In Vitro Assessment of Drug Interactions

In vitro studies indicate that eluxadoline is neither an inducer of CYP1A2, CYP2C9, CYP2C19, and CYP3A4, nor an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4 and CYP2D6 at clinically relevant systemic concentrations. Although CYP2E1 was slightly inhibited by eluxadoline (IC_{50} of approximately 20 micromolar [11 mcg/mL]), clinically meaningful interactions are unlikely. The *in vitro* studies were not adequate to establish the potential for eluxadoline to inhibit CYP3A4 in the gut *[see Drug Interactions (7)]*.

In vitro studies suggest that eluxadoline is a substrate for OAT3, OATP1B1, BSEP and MRP2, but not for OCT1, OCT2, OAT1, OATP1B3, P-gp and BCRP. Based on the *in vitro* studies, clinically meaningful interaction via inhibition of OCT1, OCT2, OAT1, OAT3, OATP1B3, BSEP and MRP2 by eluxadoline is unlikely. However, the *in vitro* studies were not adequate to establish the potential for eluxadoline to inhibit P-gp in the gut.

In Vivo Assessment of Drug Interactions

The following drug interactions were studied in healthy subjects:

Oral Contraceptives
Coadministration of multiple doses of 100 mg VIBERZI with multiple dose administration of an oral contraceptive (norethindrone 0.5 mg/ethinyl estradiol 0.035 mg) does not change the exposure of either drug.

Cyclosporine
Coadministration of a single dose of 100 mg VIBERZI with a single dose of 600 mg cyclosporine resulted in 4.4-fold and 6.2-fold increase in AUC and C_{max} of eluxadoline, respectively, compared to administration of VIBERZI alone *[see Drug Interactions (7)]*.

Probenecid
Coadministration of a single dose of 100 mg VIBERZI with a single dose of 500 mg probenecid resulted in a 35% and 31% increase in eluxadoline AUC and C_{max}, respectively, compared to administration of VIBERZI alone. This change in eluxadoline exposures is not expected to be clinically meaningful.

Rosuvastatin
Coadministration of multiple doses of 100 mg VIBERZI twice daily with a single dose 20 mg rosuvastatin resulted in an increase in the AUC (40%) and C_{max} (18%) of rosuvastatin compared to administration of rosuvastatin alone. Similar results were observed with the active, major metabolite, n-desmethyl rosuvastatin *[see Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Two-year oral carcinogenicity studies have been conducted with eluxadoline in CD-1 mice at doses up to 1500 mg/kg/day (about 14 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) and in Sprague Dawley rats at oral doses up to 1500 mg/kg/day (about 36 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg). Oral administration of eluxadoline for 104 weeks did not produce tumors in mice and rats.

Mutagenesis
Eluxadoline was negative in the Ames test, chromosome aberration test in human lymphocytes, in the mouse lymphoma cell ($L5178Y/TK^{+/-}$) forward mutation test and in the *in vivo* rat bone marrow micronucleus test.

Impairment of Fertility
Eluxadoline at oral doses up to 1000 mg/kg/day (about 10 times the human AUC of 24 ng.h/mL after a single oral dose of 100 mg) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

The efficacy and safety of VIBERZI in IBS-D patients was established in two randomized, multi-center, multi-national, double-blind, placebo-controlled trials (Studies 1 and 2). A total of 1281 patients in Study 1 and 1145 patients in Study 2 received treatment with VIBERZI 75 mg, VIBERZI 100 mg or placebo twice daily [overall, patients had a mean age of 45 years (range 18 to 80 years with 10% at least 65 years of age or older), 66% female, 86% white, 11% black, and 27% Hispanic].

All patients met Rome III criteria for IBS-D (loose [mushy] or watery stools ≥25% and hard or lumpy stools <25% of bowel movements) and were required to meet both of the following criteria:

- an average of worst abdominal pain scores in the past 24 hours of >3.0 on a 0 to 10 scale over the week prior to randomization.
- an average daily stool consistency score (Bristol Stool Scale or BSS) of ≥5.5 and at least 5 days with a BSS score ≥5 on a 1 to 7 scale over the week prior to randomization.

Pertinent exclusion criteria included: prior pancreatitis, alcohol abuse, cholecystitis prior 6 months, sphincter of Oddi dysfunction, inflammatory bowel disease, intestinal obstruction, gastrointestinal infection or diverticulitis within prior 3 months, lipase greater than 2 xULN, ALT or AST greater than 3 xULN.

Study 1 and Study 2 included identical 26-week double-blind, placebo-controlled treatment periods. Study 1 continued double-blinded for an additional 26 weeks for long-term safety (total of 52 weeks of treatment), followed by a 2-week follow-up. Study 2 included a 4-week single-blinded, placebo-withdrawal period upon completion of the 26-week treatment period. During the double-blind treatment phase and the single-blinded placebo withdrawal phase, patients were allowed to take loperamide rescue medication for the acute treatment of uncontrolled diarrhea, but were not allowed to take any other antidiarrheal, antispasmodic agent or rifaximin for their diarrhea. Additionally, patients were allowed to take aspirin-containing medications or nonsteroidal anti-inflammatory drugs for abdominal pain, but no narcotic or opioid containing agents.

Efficacy of VIBERZI was assessed in both trials using an overall composite responder primary endpoint. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by ≥30% as compared to the baseline weekly average AND a reduction in the BSS to <5 on at least 50% of the days within a 12-week time interval. Improvement in daily worst abdominal pain in the absence of a concurrent bowel movement was also considered a response day. Results for endpoints were based on electronic daily diary entries by patients.

The proportion of composite responders over 12 weeks is shown in **Table 4.** In both trials, the proportion of patients who were composite responders to VIBERZI was statistically significantly higher than placebo for both doses. The proportion of patients who were composite responders to VIBERZI was similar for male and female patients in both trials.

Table 4: Efficacy Results in Randomized Clinical Trials

	Study 1			Study 2		
	VIBERZI 100mg twice daily n=426	**VIBERZI 75mg twice daily n=427**	**PBO n=427**	**VIBERZI 100mg twice daily n=382**	**VIBERZI 75mg twice daily n=381**	**PBO n=382**
Composite[1] Response over 12 weeks						
Responder rates	25%	24%	17%	30%	29%	16%
Treatment difference	8%[2]	7%[4]		13%[3]	13%[3]	
95% CI (%)	(2.6, 13.5)	(1.4, 12.2)		(7.5, 19.2)	(6.8, 18.5)	
Composite Response over 26 weeks						
Responder rates	29%	23%	19%	33%	30%	20%
Treatment difference	10%	4%		13%	10%	
95% CI (%)	(4.7, 16.1)	(-1.0, 9.9)		(6.4, 18.8)	(4.2, 16.4)	
Abdominal Pain Response Improved ≥30% over 12 weeks						
Responder rates	43%	42%	40%	51%	48%	45%
Treatment difference	4%	3%		6%	3%	
95% CI (%)	(-3.0, 10.2)	(-3.8, 9.4)		(-1.3, 12.8)	(-4.3, 9.8)	
BSS <5 Response over 12 weeks						
Responder rates	34%	30%	22%	36%	37%	21%
Treatment difference	12%	8%		15%	16%	
95% CI (%)	(6.3, 18.2)	(2.1, 13.8)		(8.4, 21.0)	(9.7, 22.4)	

[1]Composite= Simultaneous improvement of Worst Abdominal Pain (WAP) by ≥30% and Bristol Stool Score (BSS) < 5 on the same day for ≥ 50% of days over the interval

[2] $P<0.01$

[3] $P<0.001$

[4] $P<0.05$

Additionally, the proportion of patients who were composite responders to VIBERZI at each 4-week interval was numerically higher than placebo for both doses as early as month 1 through month 6 demonstrating that efficacy is maintained throughout the course of treatment.

During the 4 week single-blind withdrawal period in Study 2, no evidence of worsening of diarrhea or abdominal pain compared to baseline was demonstrated at either dose.

16 HOW SUPPLIED/STORAGE AND HANDLING

VIBERZI is available as:

- 75 mg tablets: capsule-shaped tablets, coated in pale-yellow to light tan color, debossed with "FX75" on one side.
  Bottle of 60: NDC 0456-5375-60

- 100 mg tablets: capsule-shaped tablets, coated in pink-orange to peach color, debossed with "FX100" on one side.
  Bottle of 60: NDC 0456-5310-60

Store VIBERZI tablets at 20°C to 25°C (68°F to 77°F) with excursions permitted to 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 (Medication Guide).

Instruct patients to:

- stop VIBERZI and seek medical attention if unusual or severe abdominal pain develops, especially if they do not have a gallbladder *[see Warnings and Precautions (5.1)]*.
- avoid chronic or acute excessive alcohol use while taking VIBERZI *[see Warnings and Precautions (5.2)]*.
- take one tablet twice daily with food.
- if they miss a dose, take the next dose at the regular time. Do not take 2 doses at the same time to make up for a missed dose.
- call their healthcare provider if they are unable to tolerate VIBERZI
- discontinue VIBERZI and call their health care provider if they experience constipation lasting more than 4 days
- not take alosetron with VIBERZI or not take loperamide on a *chronic* basis with VIBERZI due to the potential for constipation. Loperamide may occasionally be used with VIBERZI for *acute management* of severe diarrhea, but must be discontinued if constipation develops. Also, instruct patients to avoid taking VIBERZI with other medications that may cause constipation (for example opioids, anticholinergics, etc.).

Manufactured by:
Patheon Pharmaceuticals, Inc
Cincinnati, OH 45237-1625 USA

Distributed by:
Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, LLC
Cincinnati, Ohio 45209 USA

MEDICATION GUIDE
VIBERZI (vye BER zee), C-X
(eluxadoline) tablets

Read this Medication Guide before you start taking VIBERZI and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

What is the most important information I should know about VIBERZI?

VIBERZI can cause serious side effects, including:

- **Sphincter of Oddi spasm.** The sphincter of Oddi is a muscular valve that controls the flow of digestive juices (bile and pancreatic juice) to the first part of your small intestine. A sphincter of Oddi spasm can cause an increase in your liver and pancreas enzymes and inflammation of the pancreas (pancreatitis) that can cause sudden stomach-area (abdomen) pain. Your risk of having a sphincter of Oddi spasm is increased if you do not have a gallbladder. This spasm usually happens within the first week of treatment with VIBERZI and usually goes away when treatment with VIBERZI is stopped.

  Stop taking VIBERZI and call your doctor if you have new or worsening stomach-area (abdomen) pain or pain in the upper right side of your stomach-area (abdomen) that may move to your back or shoulder, with or without nausea and vomiting.
- **Inflammation of the pancreas (pancreatitis).** Symptoms of pancreatitis usually go away when treatment with VIBERZI is stopped. Your risk of getting pancreatitis is increased if you drink more than 3 alcoholic drinks a day. Limit your use of alcoholic drinks while you are taking VIBERZI.

  Stop taking VIBERZI and call your doctor if you have new or worsening stomach-area (abdomen) pain that may move to your back or shoulder, with or without nausea and vomiting.

What is VIBERZI?

VIBERZI is a prescription medicine used to treat adults who have irritable bowel syndrome with diarrhea (IBS-D).

- VIBERZI is a controlled substance (CX) because it contains eluxadoline that can be a target for people who abuse prescription medicines or street drugs. Keep your VIBERZI in a safe place, to protect it from theft. Never give your VIBERZI to anyone else, because it may harm them. Selling or giving away this medicine is against the law.

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

People 65 years old and older have had an increased number of side effects, including serious side effects and stomach problems, while taking VIBERZI than people younger than 65 years old have had.

Who should not take VIBERZI?

Do not take VIBERZI if you:

- have or may have had a blockage in your gallbladder or a sphincter of Oddi problem
- have or had problems with alcohol abuse, alcohol addiction, or drink more than 3 alcoholic drinks a day
- have had inflammation of your pancreas (pancreatitis) or other pancreas problems, including if you have had or may have had a blockage in your pancreas
- have severe liver problems
- have had long-lasting (chronic) or severe constipation, or problems caused by constipation
- have or may have had a bowel blockage (intestinal obstruction)

Talk to your doctor if you are not sure if you have any of these conditions.

What should I tell my doctor before taking VIBERZI?

Before taking VIBERZI, tell your doctor about all of your medical conditions, including if you:

- See "**What is the most important information I should know about VIBERZI?**"
- do not have a gallbladder
- have liver problems
- are pregnant or plan to become pregnant. It is not known if VIBERZI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if VIBERZI passes into your breast milk or could harm your baby.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Keep a list of your medicines to show your doctor and pharmacist when you get a new medicine. VIBERZI and other medicines may affect each other causing side effects.

If you are taking VIBERZI you should not take:

- medicines that cause constipation including:
  - Lotronex® (alosetron)
  - anticholinergic medicines
  - opioid pain medicines

  Ask your doctor or pharmacist for a list of these medicines, if you are not sure.
- Avoid taking loperamide, a medicine used to treat diarrhea, for a long time (chronic use). You may take loperamide occasionally to treat severe diarrhea. **Stop taking loperamide right away if you become constipated.**

How should I take VIBERZI?

- Take VIBERZI exactly as your doctor tells you to take it.
- Take 1 tablet of VIBERZI 2 times each day with food.
- If you miss a dose, take your next dose at your regular time. Do not take 2 doses at the same time to make up for a missed dose.
- Do not change your dose or stop taking VIBERZI unless your doctor tells you to.
- If you take too much VIBERZI, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking VIBERZI?

- Limit your use of alcoholic drinks while you are taking VIBERZI.
- If you have liver problems, **do not** drive, operate machinery, or do other dangerous activities until you know how VIBERZI affects you.

What are the possible side effects of VIBERZI?

See **"What is the most important information I should know about VIBERZI?"**

The most common side effects of VIBERZI include: constipation, nausea, and abdominal pain. Stop taking VIBERZI and call your doctor if you have constipation that lasts more than 4 days.

These are not all the possible side effects of VIBERZI. 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 VIBERZI?

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

Keep VIBERZI and all medicines out of the reach of children.

General Information about the safe and effective use of VIBERZI

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use VIBERZI for a condition for which it was not prescribed. Do not give VIBERZI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about VIBERZI that is written for health professionals.

What are the ingredients in VIBERZI?
Active ingredient: eluxadoline
Inactive ingredients: silicified microcrystalline cellulose, colloidal silica, crospovidone, mannitol, magnesium stearate, and Opadry II (partially hydrolyzed polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red).

Manufactured by: Patheon Pharmaceuticals, Inc, Cincinnati, OH 45237-1625 USA
Distributed by: Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, LLC Cincinnati, Ohio 45209 USA

For more information, go to www.VIBERZI.com or call 1-800-678-1605.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: May 2015

Exhibit 5

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

920 U.S. Highway 202, P.O. Box 300
Raritan NJ 08869

21 NOV 2007

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology
Products
5901-N Ammendale Road
Beltsville, MD 20705-1266

Initial IND

IND 79,214
JNJ-27018966 tablets for oral administration

Serial No.: 000

Dear Sir/Madam:

Pursuant to the provisions of Title 21 of the Code of Federal Regulations (CFR), Part 312, Johnson & Johnson Pharmaceutical Research Development, L.L.C., herewith submits an eCTD Investigational New Drug Application (eCTD IND) for JNJ-27018966. JNJ-27018966, also known as JNJ-27018966-AAA is a mu opioid receptor agonist/delta opioid receptor antagonist being developed for the treatment of Diarrhea-predominant Irritable Bowel Syndrome (D-IBS).

The planned study (Protocol 27018966EDI1002) is an open label, randomized study to compare the pharmacokinetic profiles of 27018966 in the fed state after a high fat/high calorie breakfast versus a fasted state following the oral administration of a single 1000 mg dose in tablet form to healthy adult subjects.

To date, one study, a combined Single Ascending dose and Multiple Ascending dose study has been conducted with this compound. Protocol 27018966EDI1001 a double-blind, placebo-controlled, randomized, single and multiple ascending dose study to investigate the safety, tolerability, and pharmacokinetics of JNJ-27018966 is ongoing in the Netherlands. Sixty-six healthy subjects have already received doses of JNJ-27018966 or placebo. The drug was generally well tolerated in doses up to 2000mg.

This eCTD IND includes all required information pursuant to 21 CFR 312.23 and is in accordance with the April 2006 FDA Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.*

Please also note that tabulated overview summaries are provided with each Nonclinical summary. Individual tabulated summaries for each study are not provided; however high-level summaries of multiple studies on a single table are presented in the safety pharmacology and toxicology sections of the eCTD IND. Full tabulations of all the data are provided in the study reports.

This submission is being provided in electronic format. J&JPRD certifies that we have taken precautions to ensure that the submission is free of computer viruses and authorizes CDER to use antivirus software, as appropriate. The following software was run to check for viruses: McAfee VirusScan Enterprise 8.0.0, Virus definitions: 5146, copyright 1995-2004, Networks Associates Technology, Inc.

Johnson & Johnson Pharmaceutical Research & Development L.L.C. considers the information submitted with this application to be a trade secret and protected from disclosure under the provisions of 21 CFR §312.130.

Should you have any questions and/or comments, please contact Patricia Capaccione at:

Telephone number: 908.704-4072
Fax number: 908.725-1382
E-mail: pcapacci@prdus.jnj.com

Sincerely,

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Patricia Capaccione

Patricia Capaccione, RPh
Associate Director
Global Regulatory Affairs – Early Development

Exhibit 6

Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

December 2, 2009

Donna Griebel, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology
Products
5901-N Ammendale Road
Beltsville, MD 20705-1266

IND 79,214
JNJ-27018966 tablets for oral administration

General Correspondence
Transfer of IND Sponsorship

Serial No.: 0010

Dear Dr. Griebel:

On behalf of Johnson & Johnson Pharmaceutical Research and Development L.L.C. (J&JPRD), reference is made to IND 79,214 for JNJ-27018966 a mu opioid receptor agonist/delta opioid receptor antagonist being developed for the treatment of Diarrhea-predominant Irritable Bowel Syndrome (D-IBS). Effective with the date of this letter, Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD) is transferring sponsorship of IND 79,214 for investigational drug JNJ-27018966 to:

PPD Therapeutics, Inc.
1400 Perimeter Park Drive
Morrisville, North Carolina 27560

PPD Therapeutics, Inc. (PPD) will assume all responsibilities related to the IND and will submit a letter of acknowledgement and acceptance of responsibility.

A copy of this letter has been sent to the new responsible regulatory liaison:

Michelle Usher
Executive Director, Regulatory Affairs, NA & LA
PPD
1400 Perimeter Park Drive
Morrisville, North Carolina 27560
Phone +1 919 456 4990 / Cell +1 919 818 7565
Michelle.Usher@ppdi.com

This submission is being provided in electronic format. J&JPRD utilizes either McAfee VirusScan Enterprise or Microsoft ForeFront Client Security to ensure that this submission is free of computer viruses and spyware. J&JPRD authorizes the CDER to use similar software as appropriate.

Johnson & Johnson Pharmaceutical Research & Development L.L.C. considers the information submitted with this application to be a trade secret and protected from disclosure under the provisions of 21 CFR §312.130.

Should you have any questions and/or comments regarding this submission, please contact Patricia Capaccione at:
Telephone number: 908.704.4072

Fax number: 908.725.1382
E-mail: pcapacci@its.jnj.com

Johnson & Johnson Pharmaceutical Research & Development L.L.C.

Sincerely,

PATRICIA CAPACCIONE

Digitally signed by PATRICIA CAPACCIONE
DN: c=US, o=JNJ, ou=Employees, ou=40015, cn=PATRICIA CAPACCIONE, email=PCapacci@its.jnj.com
Reason: I am approving this document
Date: 2009.12.02 11:56:43 -05'00'

Patricia Capaccione, RPh
Associate Director, Regulatory Affairs
Global Regulatory Affairs – Early Development

Exhibit 7

PPD®

02 December 2009

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **IND 79,214; Serial No. 0011**
General Correspondence: Transfer of IND Sponsorship
JNJ-27018966

Dear Dr. Griebel:

Please be advised that effective December 2, 2009, the sponsorship of the referenced IND has been changed from Johnson & Johnson Pharmaceutical Research & Development L.L.C to PPD Therapeutics, Inc, a wholly-owned subsidiary of PPD, Inc. PPD Therapeutics confirms receipt of IND 79,214 and assumes all responsibilities associated with the IND and as described in 21 CFR 312 Subpart D. At this time, there are no clinical studies ongoing.

If you have any questions regarding this transfer of sponsorship, please do not hesitate to contact me by phone at (919) 456-4990, or by fax at (919) 456-4148.

This submission is being provided in electronic format. PPD utilizes McAfee VirusScan Enterprise (virus definition version 5820.000, dated December 2, 2009) to ensure that this submission is free of computer viruses and spyware.

Sincerely,

Michelle P. Usher

Michelle P. Usher, RAC
Executive Director, Regulatory Affairs, the Americas
PPD Development, LP

1400 Perimeter Park Drive Morrisville, NC 27560
voice +919 462 5300 fax +919 462 4148 www.ppdi.com

Exhibit 8

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 79,214

CHANGE OF SPONSOR

PPD Therapeutics, Incorporated
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
1400 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Usher:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-27018966.

Reference is also made to your December 2, 2009 submission notifying us that the sponsorship of this IND has been transferred to you from Johnson and Johnson Pharmaceutical Research & Development L.L.C. effective on December 2, 2009.

Your submission contains all the information required to complete the change in sponsorship. Our files will be updated to list you as the sponsor of this IND.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the implementing regulations (Title 21 of the Code of Federal Regulations). Those responsibilities include (1) reporting any unexpected fatal or life-threatening adverse experience associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]; (2) reporting any adverse experience associated with use of the drug that is both serious and unexpected in writing no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]; and (3) submitting annual progress reports [21 CFR 312.33].

If you have any questions, call me at (301) 796-4257.

Sincerely yours,

{See appended electronic signature page}

Diane Munro, R.N., M.B.A.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-79214	GI-1	PPD THERAPEUTICS INC	JNJ-27018966

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

/s/

DIANE H MUNRO
12/11/2009

Exhibit 9

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 079214

SPONSOR NAME/ADDRESS CHANGE

PPD Development, LP
Attention: Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
1400 Perimeter Park Drive
Morrisville, NC 27560

Dear Ms. Usher:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-27018966.

We acknowledge receipt of your March 24, 2010 correspondence notifying us that your corporate name and/or address has been changed from

PDP Therapeutics, Inc

to

Furiex Pharmaceuticals, Inc.
3900 Paramount Parkway
Suite 150
Morrisville, NC 27560

Our records have been revised to reflect this change.

If you have any questions, call me at (301) 796-4257.

Sincerely yours,

{See appended electronic signature page}

Diane II. Munro, R.N., M.B.A.
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-79214	GI-1	PPD THERAPEUTICS INC	JNJ-27018966

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

/s/

DIANE H MUNRO
03/30/2010

Exhibit 10

REGULATORY SUBMISSION AND CORRESPONDENCE CHRONOLOGY LOG

Date	Country	Application # / CT #	Serial # / Sequence	Document Type	Description of Contents
11/5/2007	USA	IND 79214	N/A	Email	Tom Moreno (FDA PM) sent pre-IND number 79,214 for JNJ - 27018966 to Patricia Capaccione (PRDUS).
11/21/2007	USA	IND 79214	0000	Initial IND	Submitted Initial IND for JNJ-27018966.
11/21/2007	USA	IND 79214	N/A	Email	P Capaccione informed T Moreno that J&J that the IND will be dispatched via the electronic gateway today. [Same email string as 05 Nov 2007.]
12/4/2007	USA	IND 79214	N/A	Letter	Official FDA letter acknowledging receipt of initial IND (SN0000).
12/18/2007	USA	IND 79214	N/A	Email	Copy of IND acknowledgement letter attached to email. [Same email string as 05 Nov 2007.]
12/21/2007	USA	IND 79214	N/A	Email	T Moreno informed P Capaccione that IND review complete and there were no clinical hold issues.
1/7/2008	USA	IND 79214	0001	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator	• Change to Protocol 27018966EDI1002; • Updated Form FDA 1572 for Protocol 27018966EDI1002.
1/24/2008	USA	IND 79214	N/A	Email	FDA letter with comments and recommendations attached to email. None were clinical hold issues.
1/24/2008	USA	IND 79214	N/A	Letter	Official letter with FDA comments and recommendations.
2/1/2008	USA	IND 79214	0002	Information Amendment: Pharmacology/Toxicology	Submitted reports for studies TOX8159 and TOX8158 at the 120 Day update.
2/14/2008	USA	IND 79214	0003	Response to Request for Information	Response to Request for Information from the FDA Communication dated 24 Jan 2008.
5/6/2008	USA	IND 79214	0004	General Correspondence	Request for Type B (End of Phase 1) Meeting.
6/4/2008	USA	IND 79214	0005	General Correspondence	Withdrawal of 06 May 2008 Type B End of Phase 1 Meeting Request.
6/10/2008	USA	IND 79214	N/A	Letter	Request to withdraw EOP1 meeting request acknowledged by FDA.

11/4/2008	USA	IND 79214	0006	Information Amendment: Pharmacology/Toxicology;#Information Amendment: Clinical	• Study reports for BA1139, BA914, TOX7686, FK6635, FK6706, FK6533, FK6533 Amendment 1, TOX8398, TOX8376; • Clinical Study Synoptic Report JNJ-27018966-EDI-1002.
2/12/2009	USA	IND 79214	0007	Annual Report	Annual Report for the Reporting Period: 21 Dec 2007 - 20 Dec 2008.
7/22/2009	USA	IND 79214	0008	Information Amendment: Pharmacology/Toxicology	Submitted reports for studies FK6432 and TOX8260.
10/12/2009	USA	IND 79214	0009	General Correspondence	Submitted Notice of Compliance Findings as provided to Div. of Scientific Investigations (12 May 2009) plus additional information from internal investigation related to BA data.
12/2/2009	USA	IND 79214	0010	General Correspondence	Transfer of IND Sponsorship to PPD Therapeutics, Inc.
12/2/2009	USA	IND 79214	0011	General Correspondence	PPD Therapeutics assumed all responsibilities for IND 79,214 effective 02 Dec 2009.
12/11/2009	USA	IND 79214	N/A	Letter	Formal notification from FDA (Diane Munro, FDA PM) that the sponsorship of the MuDelta IND has been transferred to PPD Therapeutics officially.
1/6/2010	USA	IND 79214	0012	Other	Request for End-of-Phase 1 Meeting.
1/15/2010	USA	IND 79214	N/A	Telephone Contact Report	D Munro called M Usher to inform her that FDA has granted a face-to-face EOP1 meeting on 16 Mar 2010 at 3pm. Briefing Package requested by 09 Feb 2010 (10 Desk copies).
1/15/2010	USA	IND 79214	N/A	Letter	Official letter granting EOP1 Meeting on 16 Mar 2010.
2/5/2010	USA	IND 79214	0013	Information Amendment: Chemistry/Microbiology	Submitted additional information for DS/DP, manufacturing process controls, analytical methodology, and validation and stability data. Also addressed discrepancies in original IND CMC section.
2/8/2010	USA	IND 79214	0014	Other	Submitted EOP1 Mtg Package through the Gateway plus 10 Desk copies (hardcopy) for FDA reviewers shipped to Diane Munro, Regulatory Project Manager, as requested.

2/12/2010	USA	IND 79214	0015	Other	Submitted addendum to the EOP1 Meeting Package: AE table accompanied by an explanation within the cover letter text. Sent through the Gateway plus 10 hardcopies sent to D Munro to append to existing EOP1 Mtg Desk copies.
2/16/2010	USA	IND 79214	N/A	Telephone Contact Report	M Usher called D Munro to discuss delay in delivery of EOP1 Mtg Package due to adverse weather conditions, the addendum, and potential impact of FDA closure on meeting date.
2/16/2010	USA	IND 79214	N/A	Email	M Usher supplied D Munro with her email address at Ms. Munro's request. Ms. Munro provided definitions of foreign visitors for the EOP1 Meeting on 16 Mar 2010 and instructions for filling out the attached visitor forms.
2/18/2010	USA	IND 79214	0016	Information Amendment: Pharmacology/Toxicology;#Annual Report	• Submitted Pharm/Tox study reports for TOX8103 and TOX8159; • Annual Report provided for the Reporting Period 21 Dec 2008 - 20 Dec 2009.
2/19/2010	USA	IND 79214	N/A	Email	M Usher provided Sponsor meeting attendee list. D Munro confirmed the EOP1 Meeting date as 16 Mar 2010 and acknowledged FDA receipt of meeting package desk copies. Ms. Usher confirmed that Furiex still wanted a F2F meeting and not a teleconference.
2/24/2010	USA	IND 79214	0017	Other	Provided replacement table "Summary of Adverse Events Related to Orthostasis or Syncope in Studies JNJ-27018966EDI1001 and JNJ-27018966EDI1002". Sent through the Gateway, via CD, and in hardcopy (10 Desk copies).
2/24/2010	USA	IND 79214	N/A	Telephone Contact Report	M Usher contacted D Munro regarding the summary of orthostatic AEs and to confirm the FDA meeting date of 16 Mar 2010. Ms. Munro reminded Ms. Usher about submitted forms for any non-US citizen attendees.
2/24/2010	USA	IND 79214	N/A	Email	M Usher proposed a plan for providing addendum replacement and Desk Copies to FDA. D Munro confirmed that the plan was acceptable.

3/1/2010 USA	IND 79214	N/A	Fax	Preliminary Responses to Questions for IND 79214 in preparation for the EOP1 meeting.
3/2/2010 USA	IND 79214	N/A	Telephone Contact Report	M Usher and D Munro discussed EOP1 Mtg FDA attendees and availability of draft responses from the review team.
3/9/2010 USA	IND 79214	N/A	Email	Email from M Usher to D Munro regarding nonclinical point of clarification and FDA's advice to complete Segment I fertility and early embryonic development studies in male rats prior to initiating the intended Phase 2 study.
3/24/2010 USA	IND 79214	0018	General Correspondence	Sponsor name change from PPD Therapeutics, Inc. to Furiex Pharmaceuticals, Inc., effective 22 Feb 2010.
3/30/2010 USA	IND 79214	N/A	Letter	FDA Letter acknowledged sponsor name change from PPD Therapeutics, Inc. to Furiex Pharmaceuticals, Inc.
3/30/2010 USA	IND 79214	N/A	Letter	Official End-of-Phase 1 Meeting Minutes.
3/31/2010 USA	IND 79214	0019	Information Amendment: Chemistry/Microbiology	Submitted new information regarding genotox assessment, new manufacturer, stability protocol for Phase 2 clinical lots, and loperamide placebo.
4/6/2010 USA	IND 79214	0020	Information Amendment: Clinical;#Other	Revised Investigator's Brochure Edition 4 dated 02 Mar 2010. ["Info Amend: Clinical" was selected in the SharePoint environment for searching consistency.]
4/15/2010 USA	IND 79214	0021	Protocol Amendment: New Protocol;#Protocol Amendment: New Investigator;#Information Amendment: Clinical;#Other	• Submitted new protocol 27018966IBS2001; • New investigator (new PI for 2001 study); • Revised IB dated 05 Apr 2010; and • Sponsor version of the EOP1 Meeting minutes.
4/28/2010 USA	IND 79214	0022	Protocol Amendment: Change in Protocol	Submitted amended protocol 27018966IBS2001, version 2 (dated 22 Apr 2010) and Summary of Changes.
5/24/2010 USA	IND 79214	0023	Protocol Amendment: New Investigator	Submitted new investigator information (Forms FDA 1572 and CVs) for new investigators from 16 Apr 2010 to 30 Apr 2010. [Cover letter dated 19 May 2010.]

5/27/2010	USA	IND 79214	0024	Protocol Amendment: New Protocol;#Protocol Amendment: New Investigator	• Submitted new protocol 27018966EDI1003; and • Form FDA 1572/CV for Dr. Matthew Medlock. [Cover letter dated 25 May 2010.]
6/18/2010	USA	IND 79214	0025	Protocol Amendment: New Investigator	Submitted new investigator documentation for the 2001 study.
7/8/2010	USA	IND 79214	N/A	Letter	Advice/Information Request Letter from FDA Controlled Substance Staff (CSS) signed by Dr. Griebel [reference made to 08 Feb 2010 EOP1 meeting package (SN 0014)].
7/23/2010	USA	IND 79214	0026	Protocol Amendment: New Investigator;#Information Amendment: Pharmacology/Toxicology;#Other	• Submitted new investigator information for study 27018966IBS2001; • Nonclinical tox reports AC34AZ.341.BLT In Vitro Chromosome Aberration Test & AC34AZ.503.BTL Bacterial Reverse Mutation Assay; • Changed US Agent to M Usher; and Updated Transfer of Obligation (TORO) for Protocols 27018966IBS2001 & 27018966EDI1003. [Cover letter dated 16 Jul 2010.]
8/3/2010	USA	IND 79214	0027	Protocol Amendment: Change in Protocol	Submitted Protocol 27018966IBS2001 amendment 2, version 3 (dated 27 Jul 2010).
8/20/2010	USA	IND 79214	0028	Protocol Amendment: New Investigator	Submitted both new and revised investigator information for study 27018966IBS2001.
9/15/2010	USA	IND 79214	N/A	Email	Email contact report (between NLM & PPD Regulatory) regarding notice and resolution of Patient Recruitment Services number function at www.clinicaltrials.gov for NCT01130272. Issue was identified and resolved on 15 Sep 2010.
9/17/2010	USA	IND 79214	0029	Protocol Amendment: New Investigator	Submitted both new and revised investigator information for study 27018966IBS2001.
9/30/2010	USA	IND 79214	0030	Information Amendment: Pharmacology/Toxicology;#General Correspondence	• Submitted unaudited, draft nonclinical study report 1808-003; • Notified Agency that Furiex was lifting restriction of <100 males to protocol 27018966IBS2001 without submitting formal protocol revision.

10/29/2010 USA	IND 79214	0031	Other	Request for Fast Track designation.
11/2/2010 USA	IND 79214	N/A	Letter	Acknowledgement of receipt of Fast Track Request by B Strongin (Chief, Project Mgmt. Staff).
11/5/2010 USA	IND 79214	0032	Safety Report: Initial	Initial written safety report for Subject ALM/047-0003 for acute pancreatitis in study 27018966IBS2001 (Mfr. Control No. 2010JJ000017).
11/12/2010 USA	IND 79214	0033	Protocol Amendment: New Investigator;#Information Amendment: Chemistry/Microbiology;#General Correspondence	• Submitted new investigator information; • Updated CMC information related to drug substance, JNJ-27018966 tablets, and placebo tablets; and • Furiex acknowledged receipt of FDA Advice/Information Request Letter (dated 08 Jul 2010) regarding abuse potential studies.
11/18/2010 USA	IND 79214	0034	Safety Report: Follow-up	Follow-up safety report (1) for 2010JJ000017
11/30/2010 USA	IND 79214	0035	Safety Report: Follow-up	Follow-up safety report (2) for 2010JJ000017
12/21/2010 USA	IND 79214	N/A	Letter	Notification made to Division of Scientific Investigations of early termination of Dr. Blumenthal's site (Aventura, FL).
12/22/2010 USA	IND 79214	0036	Protocol Amendment: New Investigator;#Safety Report: Follow-up	• Submitted new and revised investigator information for 27018966IBS2001; and • Follow-up safety report (3) for 2010JJ000017
12/27/2010 USA	IND 79214	0037	Other	Notice of intent to request carcinogenicity special protocol assessments (SPA).
1/5/2011 USA	IND 79214	0038	Safety Report: Follow-up	Follow-up safety report (4) for 2010JJ000017
1/19/2011 USA	IND 79214	N/A	Email	B Strongin transmitted copy of FDA letter granting Fast Track designation via email.
1/19/2011 USA	IND 79214	N/A	Letter	FDA Letter Granting Fast Track designation.

1/21/2011 USA	IND 79214	0039	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator;#Information Amendment: Pharmacology/Toxicology;#Information Amendment: Clinical	• Protocol 27018966IBS2001 amend. 3, version 4 (dated 6-Jan-2011); • New and revised investigator information for study 27018966IBS2001; • Nonclinical study report 1808-003 (Seg I), and • Updated Investigator's Brochure, edition 6 (dated 19 Jan 2011).
1/28/2011 USA	IND 79214	N/A	Letter	M Usher sent the FDA Div. of Scientific Investigations notification of early termination letter for Dr. VanGinkel's site (South Miami, FL).
2/8/2011 USA	IND 79214	0040	Other	Request for Special Protocol Assessment: Carcinogenicity - Rat (JNJ-27018966-AAA: 104-Week Oral Carcinogenicity Study in Rats, Study Number 1808-008). [Cover letter dated 04 Feb 2010.]
2/8/2011 USA	IND 79214	0041	Other	Request for Special Protocol Assessment: Carcinogenicity - Mouse (JNJ-27018966-AAA: 104-Week Oral Carcinogenicity Study in Mice, Study Number 1808-009). [Cover letter dated 04 Feb 2010.]
2/16/2011 USA	IND 79214	N/A	Letter	FDA acknowledged receipt of Carcinogenicity SPA for Rat and committed to provide a response within 45 days.
2/21/2011 USA	IND 79214	0042	Protocol Amendment: New Investigator;#Information Amendment: Chemistry/Microbiology;#Information Amendment: Clinical;#Annual Report	• Submitted new and revised investigator information for 27018966IBS2001; • CMC (drug product and QOS update); • Clinical Study Report 27018966EDI1003; and • Annual Report for the Reporting Period: 21 Dec 2009 - 14 Dec 2010.
3/16/2011 USA	IND 79214	N/A	Fax	Response to Carcinogenicity Special Protocol Assessment Requests - Final CAC Report (for both Mouse and Rat Carcinogenicity SPAs).
3/18/2011 USA	IND 79214	0043	Protocol Amendment: New Investigator	Submitted revised investigator information for 27018966IBS2001.

4/21/2011	USA	IND 79214	0044	Protocol Amendment: New Investigator	Submitted new and revised investigator information for 27018966IBS2001.
5/13/2011	USA	IND 79214	0045	Other	Submitted Type C meeting request: Endpoint guidance.
5/20/2011	USA	IND 79214	0046	Other	Type C Meeting briefing package for Endpoint Guidance.
5/24/2011	USA	IND 79214	0047	Protocol Amendment: New Investigator	Submitted revised investigator information for 27018966IBS2001.
5/27/2011	USA	IND 79214	N/A	Letter	Type C meeting request granted. Meeting scheduled for 05 July 2011, face to face. Letter included list of FDA meeting attendees, request for Sponsor attendees, and visitor forms and instructions.
6/3/2011	USA	IND 79214	0048	Other	Submitted revised Type C Meeting Briefing Package because of rounding errors that were detected following submission of SN0046. Revised Desk copies (13) for the Type C (Endpoints) Meeting were sent to B Strongin to incorporate these revisions.
6/17/2011	USA	IND 79214	0049	Protocol Amendment: New Investigator	Submitted new and revised investigator data for 27018966IBS2001.
6/27/2011	USA	IND 79214	N/A	Email	M Usher provided the Sponsor attendee list for the Type C meeting and asked if a short presentation was possible. FDA will have a projector available but instructed to limit number of slides.
6/29/2011	USA	IND 79214	N/A	Email	B Strongin provided FDA preliminary responses to Type C (Endpoints) meeting questions and inquired about product ownership.
6/30/2011	USA	IND 79214	N/A	Email	M Usher clarified relationship between J&J and Furiex in regard to MuDelta and confirmed that Furiex would still like to hold the meeting even with receipt of preliminary responses. [Same email as 29 Jun 2011.]
7/6/2011	USA	IND 79214	N/A	Email	M Usher provided B Strongin with a copy of the clarification slides presented by Furiex at the Type C meeting on 05 July.
7/15/2011	USA	IND 79214	0050	Protocol Amendment: New Investigator	Submitted revised investigator information for 27018966IBS2001.

7/27/2011 USA	IND 79214	0051	Other	Submitted Sponsor minutes from the 05 July 2011 Type C meeting minutes, including the slide deck and FDA preliminary responses.
8/2/2011 USA	IND 79214	0052	Other	Submitted Type B End of Phase 2 (clinical) meeting request.
8/2/2011 USA	IND 79214	N/A	Email	B Strongin transmitted copy of FDA Type C (Endpoints) meeting minutes via email.
8/2/2011 USA	IND 79214	N/A	Letter	FDA's Type C (Endpoints) meeting minutes.
8/15/2011 USA	IND 79214	0053	Protocol Amendment: New Investigator;#Information Amendment: Pharmacology/Toxicology	• Submitted revised investigator information for 27018966IBS2001; and • Nonclinical study reports 1808-004, 1808-006, and 1808-007.
8/16/2011 USA	IND 79214	N/A	Email	B Strongin transmitted letter granting EOP2 meeting via email and requested M Usher provide Sponsor questions in Word.
8/16/2011 USA	IND 79214	N/A	Letter	Official EOP2 Meeting Granted Letter.
8/30/2011 USA	IND 79214	0054	Other	• Submitted Type B EOP2 Meeting Briefing Package. • Desk copies of the Briefing Package (SN0054) were sent under separate cover to B Strongin on 29 Aug 2011.
9/1/2011 USA	IND 79214	N/A	Email	M Usher provided B Strongin with EOP2 questions in Word format as requested.
9/16/2011 USA	IND 79214	N/A	Email	M Usher confirmed that the Furiex attendees have not changed, confirmed length of meeting, and requested status of FDA preliminary responses. B Strongin confirmed meeting length is 1 hour and responses should be available later next week.
9/22/2011 USA	IND 79214	N/A	Email	M Usher followed up on the status of the preliminary responses. B Strongin anticipated they would be available 22 Sept or 23 Sept.
9/23/2011 USA	IND 79214	0055	Protocol Amendment: New Investigator	Submitted revised investigator information for 27018966IBS2001.
9/23/2011 USA	IND 79214	N/A	Email	M Usher followed up again on the status of the preliminary responses. B Strongin informed Ms. Usher that he was still waiting for responses but should have them later in the day.

9/23/2011	USA	IND 79214	N/A	Email	B Strongin transmitted FDA Preliminary Comments for End of Phase 2 Meeting questions via email. He informed M Usher that the EOP2 meeting is 50 minutes in length so Furiex must decide which questions they want to discuss during the meeting.
9/23/2011	USA	IND 79214	N/A	Letter	FDA Preliminary Comments for End of Phase 2 Meeting questions.
9/27/2011	USA	IND 79214	N/A	Email	M Usher informed B Strongin that Furiex wanted to focus on the Agency's clinical responses for the EOP2 meeting and provided a list. Also provided the Furiex EOP2 slide set for use during the meeting.
9/30/2011	USA	IND 79214	N/A	Email	M Usher requested names of FDA attendees at the EOP2 meeting for inclusion in the Sponsor meeting minutes.
10/3/2011	USA	IND 79214	N/A	Email	B Strongin provided names of FDA attendees to M Usher.
10/4/2011	USA	IND 79214	0056	Information Amendment: Clinical	• Submitted datasets from Phase 2 Protocol 27018966IBS2001; and • Responded to Request for Additional Information regarding daily versus weekly responder definitions.
10/6/2011	USA	IND 79214	N/A	Email	B Strongin requested statistical information: 1) dataset for daily responder for pain and BSS, 2) program used to generate tables in the 04 Oct submission, and 3) protocol and SAP for Phase 2 protocol or a link to this information.
10/10/2011	USA	IND 79214	0057	Letter;#Information Amendment: Clinical	Responded to Request for Additional Information by submitting the Statistical Analysis Plan (SAP), version 5.0, for Protocol 27018966IBS2001.
10/12/2011	USA	IND 79214	0058	Other	• Submitted additional datasets from Phase 2 study supporting daily responder definition in response to Request for Information; and • Provided Sponsor version of the EOP2 Meeting Minutes (which included FDA preliminary comments to 27 Sep 2011 EOP2 mtg).
10/25/2011	USA	IND 79214	0059	General Correspondence	Follow-up to action item from EOP2 meeting regarding investigator access to IVR as related to the FDA Guidance on Patient-Reported Outcome (PRO) measures.

10/25/2011 USA	IND 79214	N/A	Email	M Usher requested status for receipt of the FDA EOP2 meeting minutes.
10/26/2011 USA	IND 79214	N/A	Email	B Strongin transmitted EOP2 meeting minutes via email to M Usher.
10/26/2011 USA	IND 79214	N/A	Letter	Official FDA Meeting Minutes for IND 79,214 EOP2 meeting on 27 Sep 2011.
10/31/2011 USA	IND 79214	N/A	Email	M Usher confirmed receipt of the official minutes and commented that: 1) the sponsor slides should be part of the meeting minutes since they are referred to in the meeting minutes, and 2) there appear to be general template text remaining in Sections 4 and 5 that are incomplete.
11/2/2011 USA	IND 79214	N/A	Email	M Usher followed up again on requested changes to the Agency meeting minutes following receipt of the hard copy minutes, and inquired whether Furiex requests for revisions would be accommodated. B Strongin replied that he was in the process of revising the minutes and should be able to send them in a few days.
11/16/2011 USA	IND 79214	N/A	Email	M Usher followed up again with B Strongin regarding the status of the EOP2 meeting minutes.
11/17/2011 USA	IND 79214	N/A	Email	B Strongin apologized for the delay and stated that he hoped to have the official minutes revised within a few days.
11/18/2011 USA	IND 79214	0060	Other	Submitted request for Type B End-of-Phase 2 CMC Meeting.
12/1/2011 USA	IND 79214	N/A	Email	M Usher inquired about the status of the EOP2 meeting minutes given B Strongin's estimate of 17 Nov 2011, i.e., that the minutes would be completed within a few days.
12/8/2011 USA	IND 79214	N/A	Email	M Usher again requested the EOP2 meeting minutes and stated that the need for the minutes is urgent to ensure the Phase 3 protocols meet FDA's understanding of the meeting agreements. Also informed B Strongin that Furiex would like to begin using the Development Safety Update Report (DSUR), in lieu of the IND Annual Report, for the upcoming report due in Feb 2012.

12/9/2011	USA	IND 79214	N/A	Email	B Strongin transmitted the final Agency version of the EOP2 meeting minutes as an email attachment. Also, provided instructions to Furiex regarding the procedure for transitioning to the DSUR in lieu of the IND Annual Report.
12/9/2011	USA	IND 79214	N/A	Letter	Official Agency minutes of the EOP2 meeting with Furiex on 27 Sept 2011.
12/13/2011	USA	IND 79214	N/A	Telephone Contact Report	M Usher spoke with Catherine Tran-Zwanetz (Division of New Drug Quality Assessment) regarding the Furiex request for End of Phase 2 CMC meeting. The Agency proposed a meeting on 30 Jan 2012 at 2pm. Ms. Tran-Zwanetz requested Furiex confirm acceptability by email.
12/13/2011	USA	IND 79214	N/A	Email	M Usher confirmed CMC EOP2 Meeting for 30 Jan 2012. Also committed to submit the Briefing Package electronically at least 4 weeks prior to the meeting along with 6 Desk copies to C Tran-Zwanetz's attention.
12/19/2011	USA	IND 79214	0061	Other	Formal request to use the Development Safety Update Report with an International Development Birthdate in lieu of the IND Annual Report.
12/20/2011	USA	IND 79214	N/A	Letter	Agency granted request to use a harmonized DSUR, with the same reporting period as the IND Annual Report, i.e., 22 December to 21 December.
12/28/2011	USA	IND 79214	0062	Other	Submitted Type B End of Phase 2 CMC Meeting Package for the meeting scheduled with the Division on 30 Jan 2012.
1/4/2012	USA	IND 79214	N/A	Email	C Tran-Zwanetz acknowledged receipt of the meeting package Desk copies and requested questions in Word. M Usher provided and asked if the Agency needed additional information.
1/4/2012	USA	IND 79214	N/A	Email	C Tran-Zwanetz stated that no additional information was needed for the EOP2 CMC meeting.
1/24/2012	USA	IND 79214	N/A	Email	C Tran-Zwanetz transmitted to M Usher, via email, the Agency's preliminary responses to Furiex' questions (dated 18 Nov 2011) in advance of the EOP2 CMC meeting on 30 Jan 2012. Ms. Tran-Zwanetz requested that Furiex inform the Agency should the meeting no longer be necessary.

1/24/2012	USA	IND 79214	N/A	Letter	Official letter with FDA preliminary responses for the EOP2 CMC meeting on 30 Jan 2012.
1/25/2012	USA	IND 79214	N/A	Email	M Usher notified C Tran-Zwanetz that, after reviewing the Agency's thorough responses, Furiex no longer needs to hold the CMC EOP2 meeting on 30 Jan 2012 as originally planned and requested to cancel the meeting.
1/31/2012	USA	IND 79214	N/A	Letter	M Usher sent the FDA Office of Scientific Investigations notification regarding issues of misconduct by the former study coordinator at Dr. Amann's site (Tupelo, MS). All issues have been reported to the North Mississippi Health Services IRB.
2/17/2012	USA	IND 79214	0063	Information Amendment: Pharmacology/Toxicology;#Information Amendment: Clinical;#Annual Report;#DSUR	• Submitted nonclinical toxicokinetic study reports FK10138, FK10141, and FK10142; • Updated Investigator's Brochure, edition 7 (dated 06 Feb 2012); and • DSUR 01 for the Reporting Period: 15 Dec 2010 - 20 Dec 2011, in lieu of an IND Annual Report.
3/14/2012	USA	IND 79214	0064	Protocol Amendment: New Protocol;#Information Amendment: Clinical;#General Correspondence	• Submitted new protocols for studies 27018966IBS3001 and 27018966IBS3002 and requested confirmation that they are acceptable to the Agency as pivotal trials for the IBD-d indication. • Also submitted the final clinical study report for the 27018966IBS2001 study. • Requested waiver for compliance with 21 CRF Part 56 for all ex-US sites participating in the 3001 & 3002 studies.
4/13/2012	USA	IND 79214	0065	Other	In follow-up to the 27 Oct 2011 EOP2 Meeting, Furiex requested Agency comment on the timelines for both the study conduct and review of the draft protocol design of the Phase 1 renal impairment study.

4/27/2012	USA	IND 79214	N/A	Email	M Usher followed up with B Strongin on serial submission 0064 (08 Mar 2012) which contained the final Phase 3 protocols for Mu Delta. She asked whether the Agency has any comment on the question that was submitted with the protocols to ensure compliance with the agreements made during the EOP2 meeting.
5/7/2012	USA	IND 79214	N/A	Telephone Contact Report	M Usher followed up with B Strongin regarding status of review of Serial Submission 0064.
5/14/2012	USA	IND 79214	N/A	Email	M Usher followed up with B Strongin regarding status of review of Serial Submission 0064.
5/18/2012	USA	IND 79214	N/A	Email	M Usher followed up with B Strongin regarding status of review of Serial Submission 0064.
5/21/2012	USA	IND 79214	0066	Other	Type C Meeting Request/Briefing Document: Request for written responses only from CSS regarding oral/snorting studies and impact on scheduling; in vitro tamperability/extractability plans.
5/21/2012	USA	IND 79214	N/A	Email	M Usher followed up with B Strongin regarding status of review of Serial Submission 0064.
5/22/2012	USA	IND 79214	N/A	Letter	FDA Advice/Information Request Letter: FDA granted IRB waiver for P3 studies and provided statistical comments on Phase 3 protocols (formal response to Serial Submission 0064).
5/22/2012	USA	IND 79214	N/A	Email	B Strongin provided FDA's response to Serial Submission 0064.
5/24/2012	USA	IND 79214	N/A	Email	M Usher denotes that FDA failed to respond to question submitted in SSN 0064 regarding P3 protocols, i.e., are the studies in compliance with EOP2 agreements and acceptable as pivotal studies.
5/25/2012	USA	IND 79214	N/A	Email	B Strongin replied that FDA cannot respond to question in serial submission 0064 until they have received responses to statistical questions (see Advice/Information Request Letter dated 22 May 2012).

5/31/2012	USA	IND 79214	0067	Other	Furiex reply to statistical comments from FDA letter 22 May 2012 and addresses impact of revised FDA IBS Guidance on P3 program.
5/31/2012	USA	IND 79214	N/A	Email	B Strongin indicated FDA should have responses to Serial Submission 0065 by end of June 2012.
5/31/2012	USA	IND 79214	N/A	Email	M Usher requested status of FDA review of Serial Submission 0065 (renal protocol).
5/31/2012	USA	IND 79214	N/A	Letter	FDA Granted Meeting (written responses only) with CSS (see Serial Submission 0066). Letter transmitted via email.
6/11/2012	USA	IND 79214	0068	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator;#Information Amendment: Chemistry/Microbiology;#Information Amendment: Clinical	Amendment 1 for Protocols 3001 and 3002. New Investigator added for 3001 (Ajani, D) and 3002 (Allaw, Mohammed A). SAPs for 3001 and 3002. CMC Info Amendment to support Phase 3 CTM.
6/11/2012	USA	IND 79214	N/A	Letter	FDA Responds to Serial Submission SN0065 regarding the Phase 1 Renal Study.
6/13/2012	USA	IND 79214	N/A	Letter	FDA responds to Serial Submission SN0064 & SN0067 indicating statistical responses were acceptable, proposed P3 studies are pivotal and comply with EOP2 agreements, and are not impacted by final publication of IBS guidance.
6/28/2012	USA	IND 79214	0069	Protocol Amendment: New Protocol	Submission of New Phase 1 Hepatic Protocol, 27018966CPS1005

				Study 3001: Aggarwal, Alfonso, Anderson, Andrews, Arora A, Arora C, Arslanian, Ayesu, Baber, Baird, Baker, Ballinger, Banks, Barber, Barish, Barnett, Bedel, Bekal, Ben Zvi, Bland, Blankfield, Blecker, Blumberg, Bohman, Bolster, Brandon, Buth, Canaan, Carr, Carrigan, Chappel, Cheung, Chintalapani, Clark, Coppola. Jr., Dellon, DeSantis, Desta, DiGiovanna, Dinh, DiSarli, Dulitz, Dunmyer, Dunn, Ellison, Epstein, Eskreis, Fein, Ferrera, Figueroa, Finneran, Florez, Fritz, Gaspari, Gatof, Gladstein, Godwin, Goff, Goldstein, Gonte, Gonzalez, Guthrie, Hagan, Harlan, Harper, Harris, Harris, Harwitt, Hassani, Hellstern, Jr., Hendrix, Heurich, Holder, Horn, Howell, Huffman, Iyer, Izanec, Jackson, Jacobs, Jain, Jamal, James, Jimenez, Johnson, Jr., Jones, Joyce, Kalafer, Karn, Kastelic, Kelehan, Kemp, Kessel, Kim, Kimmel, Kimzey, King, Kirstein, Koch, Kowaloff, Krause, Krumian, Kumar, Laurent, Leggett, Lesh, Levy, Jr., Lijewski, Lillestol, Lillo, Lodewick, Lorch, Jr., Lowe, Lumicao, Mahood, Makam, Malik, Marilley, Marple, McCarroll, McGill, Medoff, Medwedeff, Meisner, Menasha, Merkes, Merrick, Meyer, Miranda, Moretti, Moulton, Movafagh, Murphy, Nagrani, Navayogarajah, Neuman, Ogunbi, Ojuri, Oskin, Palatnik, Palchick, Palmer, Patel, Patton, Perez, Peters, Petro, Pfeifer, Phillips, Poulos, Presant, Pressman, Price-Miller, Pulver, Purighalla, Race, Rao, Reina, Ricci, Rubino, Rudolph, Schmidt, Schwender, Scowcroft, Seaton, Seidner, Semeko, Sensenbrenner, Shah, Shah, Shah, Shockey, Shoemaker, Slandzicki, Srinivasan, Stein, Tarleton, Tatum, Taunk, Teixeira, Teniola, Thebaud, Thompson, Tidman, Turner, Vaid, Velazquez, Wagner, Walker, Weinstein, Weprin, Williams, Wilson D, Wilson S, Woyshville, Wukelic
7/3/2012 USA	IND 79214	0070	Protocol Amendment: New Investigator	
7/11/2012 USA	IND 79214	0071	Letter;#Information Amendment: Clinical;#Other	Request for Comment on Redesign of Phase 1 Program. Submission of Transporter Study Reports (OPT-2012-063 and OPT-2012-064)
7/23/2012 USA	IND 79214	N/A	Email	Email from B. Strongin (FDA) to M. Usher indicating that CSS will need more time to respond to SN 0066 submitted on 21 May 2012 and can not respond before 17 Aug 2012

7/24/2012	USA	IND 79214	N/A	Email	Email from B. Strongin (FDA) to M. Usher requesting that the questions in the SN 0066 be sent in MS Word format to be able to prepare the CSS responses.
7/25/2012	USA	IND 79214	0072	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator	Amendment 1 to Hepatic protocol, 27018966CPS1005. Submitted 1572s and CVs for Investigators Galloway and Farbakhsh
7/25/2012	USA	IND 79214	N/A	Email	Email response from M. Usher to B. Strongin (FDA) providing the SN 0066 questions in Word format as requested on 24 July 2012

				"Submitted New 1572 and CVs for Study 27018966IBS3001 (Adler, Alexander, Archibald, Barnett, Benson, Collins, Cova, Crespo, du Preez, Dykes, Jr., Eisner, Gleason, Godsell, Gutman, Hardi, Hartvickson, Hoekstra, Infusino, Jayanty, Kamyar, Koehler, Lukes, Mapel, Miller, Neutel, Pang, Parker, Jr., Patel, Reddy, Reisman, Riccio, Salem, Silvera, Stollman, Sutter, Thompson, Jr., Wyman); Revised 1572s for Andrews, Ballinger and Clark. Submitted New 1572/CVs for Study 27018966IBS3002 (Ahmad, Aran-Serrano, Bhushan, Baer, Black, Bochner, Cha, Chiba, Clark, Dar, Diffee, D'Ignazio, Dupree, Durbin, Dzongowski, Elkhashab, Farris, Fisk, Galvez, Gorgi-Mikhail, Graif, Gunaratnam, Heiman, Henein, Joshi, Karnam, Kaufmann, Klein, Koval, Lang, Lapham, Lassiter, Lichtenstein, Madonia, Martin, McGuire Jr, Miner, Jr., Minkowitz, Mirhej, Montanez, Morelli, Muller, Jr., Munoz, Nwora, Olusola, Poindexter, Pouzar, Rogers, Saeed, Salter, Schumacher, Seep, Seljuki, Siddiqui, Silver, Stewart, Jr., Suiter, Taber, Tuteja, Updegrove, Vaughn, Zimmerman); Revised 1572s for Ball, Brody, Foley, Strzinek
8/3/2012 USA	IND 79214	0073	Protocol Amendment: New Investigator	
8/10/2012 USA	IND 79214	N/A	Email	FDA confirms CSS responses to SN 0066 will be provided around 17 Aug 2012
8/13/2012 USA	IND 79214	N/A	Email	FDA confirms responses for SN 0071 will be provided around 20 September 2012
8/25/2012 USA	IND 79214	0074	Protocol Amendment: New Protocol;#Information Amendment: Clinical	Submission of the OC DDI Protocol 27018966CPS1007 and the synoptic CSR for the Phase 1 SAD/MAD study 27018966EDI1001
8/30/2012 USA	IND 79214	0075	Protocol Amendment: New Protocol	Submission of QTc protocol27018966CPS1008 to IRT

8/31/2012	USA	IND 79214	N/A	Letter;#Email	FDA provides CSS responses to SN 0066. No IV or oral HAL study needed. Wants IN BA or clinical study if safe. Does not provide response to Question 10 regarding adequacy of the CMC in vitro plan to address tamperability/extractability.
8/31/2012	USA	IND 79214	N/A	Email	Furiex attempting to get status of CSS responses of SN 0066
9/4/2012	USA	IND 79214	N/A	Email	Furiex alerts FDA by phone and email that the CSS responses received on 31 Aug 2012 were incomplete and missing response to Question 10.

				27018966IBS3002. New Investigator and Revised Investigator information For 3001: New: Ayesu, Gonte, Holder, Horn, Jayanty, Slandzicki, Thompson Revised: Alaradi, Albert, Almaguer, Apseloff, Bernstein, Block, Boagni, Claassen, Cohen, Dhillon, Drosman, Dryden, Jr., Essink, Evans, Gonzalez, Green, Heigerick, Hullett, Kolettis, Lomboy, Lynch, Mascaro, Morrar, Patel, Reyes, III, Rhudy, Salvato, Scarsella, Schwarz, Stedman, Swauger, Thomas, Varunok, Yeoman, Zachow, Zuckerman For 3002: New: Bhandari, Bochner, Hemaidan, House, Ptak, Reynolds, Salter, Sligh Revised: Baxter, Bissette, Brown, Caves, Chilvers, Cowan, Davis, Dewan, Elsen, Essink, Feldman, Gimness, Greaney, Grudell, Horwitz, Johary, Johnson, Jones, Kearney, Kennedy, Lacy, Lewy-Alterbaum, McNeil, Moses, O'Barr, Olivarez, Jr., O'Mahony, Patel, Peniston, Pineda-Velez, Pluto, Samano, II, Singleton, Sirakoff, Souaid, Stacey, Syed, Tang, Troyan, Varano, Vo, Wilson, Yassear
9/5/2012	USA	IND 79214	0076	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator
9/6/2012	USA	IND 79214	N/A	Email	Second attempt to reach FDA regarding missing response to Q10 in CSS responses to SN 0066
9/9/2012	USA	IND 79214	N/A	Email	B. Strongin (FDA) replies that he was on vacation and will follow up regarding status of CSS response to Question 10 (from SN 0066)

9/13/2012	USA	IND 79214	N/A	Email	M. Usher replies to B. Strongin's email of 13 Sep 2012 indicating that the to-be-marketed formulation was described in the meeting package and that CSS should be able to provide a more comprehensive response. Additionally she notes that much of the information that CSS noted in their response was already addressed in the meeting package provided to CSS on 21 May 2012 (dated 18 May 2012).
9/13/2012	USA	IND 79214	N/A	Email	B. Strongin (FDA) provides CSS response to Question 10. Also he denotes that the reviewer responsible for the Phase 1 re-design review is on leave and to check back end of the following week (21 Sep) for status.
9/18/2012	USA	IND 79214	0077	Safety Report: Initial	Initial IND Safety Report 2012JJ000009 (Elevated ALT/AST)
9/18/2012	USA	IND 79214	N/A	Email	B. Strongin (FDA) replies indicating that CSS is preparing a response to concerns raised in M.Usher's 13 Sep 2012 email. He also notes that FDA expects to get us comments back on Phase 1 redesign submission within two weeks (w/c 01 Oct 2012)
9/28/2012	USA	IND 79214	N/A	Email	B. Strongin provides outstanding CMC CSS response to Question 10 (SN 0066)
9/28/2012	USA	IND 79214	N/A	Email	B. Strongin provides anticipated timelines for FDA IRT review of QTc protocol (SN 0075)

10/8/2012	USA	IND 79214	0078	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator	Revised Protocol for 27018966CPS1007 (Amendment 1); Revised Investigators: 3001:Barnett R, Ben Zvi J, Gaspari M, Hartvickson R, Hellstern P, Jackson R, Kelehan S, Koehler T Krumian R, Marple R, Poulos J, Sensenbrenner J, Shah A ; 3002: Acosta I, Armas E, Bassan I, DeSantis M, Galvez O, Dewan M, Janovitz R, Johnston J, Nichol B, Simpson RI, Tessler D, Wallace J, Wine A. New Investigators: 1007: Vince B; 3001:Focil A, Fraser H, Hudnut A, Nickl N, Paine W, Radin D, Wo J, Wohlman R; 3002: Allen G, Carpenter K, Dorn S, Elbanna K, Lembo A, Maier J, Michon A, Misik K, Montgomery R, Mosley R, Nguyen T, Olafsson S, Pratha V, Sosa-Padilla M, Springsteen P, Torres O, Weinberg P
10/10/2012	USA	IND 79214	N/A	Email	Email correspondence between M. Usher and B. Strongin on status of FDA responses on Phase 1 Redesign (SN 0071)
10/10/2012	USA	IND 79214	N/A	Letter	FDA Clin/Pharm Responses to Phase 1 Redesign proposed in SN 0071
10/13/2012	USA	IND 79214	N/A	Email	Email correspondence between M. Usher and B. Strongin regarding alerting QTIRT regarding comment contained in the 10Oct2012 response letter regarding draft QTC protocol that is still under review
10/19/2012	USA	IND 79214	0079	Safety Report: Follow-up	Follow-up report (1) for 2012J000009 (Elevated Liver Enzymes)
10/24/2012	USA	IND 79214	0080	Safety Report: Initial	Initial Safety Report for 2012J0000011 (Elevated ALT/AST)

10/25/2012	USA	IND 79214	0081	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator;#Information Amendment: Pharmacology/Toxicology	Submission contains: Protocol Amendment 2 for 27018966CPS1007; Revised Investigator data for Farbakhsh K (CPS1005), Jones M, Lillestol M, Moretti J, and Schimidt J (Study IBS3001); New Investigator data for IBS3001: Ainsworth, Blagden, Brunskill, Cannon, Fairhead, Fruchter, Gaunt, Green, Jones, Kerrane, Langan, Lentz, Nompleggi, Schey, Shetler, Yazd; New Investigator data for IBS3002: Abousaif, Brown, Butler, Felber, Halwan, Hess, Jones, Lumb, Michael, Reed, Smith. Information Amendment to include amended reports for DD07334 and DD07374.
10/26/2012	USA	IND 79214	0082	Safety Report: Initial	Initial Safety Report for 2012J0000013 (Altered Mental State)
10/29/2012	USA	IND 79214	N/A	Email	Email correspondence from Anissa Davis indicating that she is taking over as the FDA Project Manager for IND 79,214 and that she expects to send us comments on the QTc protocol within 2 weeks
11/2/2012	USA	IND 79214	0083	Safety Report: Follow-up	Follow up safety report (1) for 2012JJ000013
11/2/2012	USA	IND 79214	N/A	Letter;#Response to Request for Information	FDA provides comments on QTc protocol (serial submission 0075)
11/9/2012	USA	IND 79214	0084	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator;#Information Amendment: Pharmacology/Toxicology;#Information Amendment: Clinical	Amendment 3 (Version 4) to protocols 3001 and 3002. Information Amendment for revised IB (version 8) to change RSI for elevated transaminases and respiratory depression. New investigators added to 3001 (Adam) and 3002 (Chuka). Pharm/Tox Amendment to include the submission of final reports for IV tox (1808-013, 1808-014, 1808-015 and1808-012) and pulmonary safety pharm report (1808-016)
11/9/2012	USA	IND 79214	0085	Safety Report: Follow-up	Follow-up safety report (1) for 2012JJ000011 and Follow-up safety report (2) for 2012JJ000009

11/16/2012	USA	IND 79214	0086	Protocol Amendment: Change in Protocol;#Information Amendment: Clinical	Submission of revised protocol for 27018966CPS1007 (amendment 3, version 4). Submission of revised SAPs (version 2.6) for studies 27018966IBS3001/3002
11/20/2012	USA	IND 79214	0087	Safety Report: Follow-up	Follow up safety report (3) for 2012JJ000009
11/30/2012	USA	IND 79214	0088	Protocol Amendment: New Investigator	New Investigators Submitted to Protocol 27018966CPS1005: Berg; Protocol 27018966IBS3001: Adams, Arebi, Barnes, Bundy, Cahill, Caldwell, Corey, Culpepper, Dantzler, Eavis, Falk, Hejeebu, Hoque, Levine, McLaughlin, Nguyen, Prather, Sternlicht, Stroud, Tomlinson; Protocol 27018966IBS3002: Dhar, Eugenicos, Iqbal, Keld, Kippen, Lee, Middleton, Olden, Rall, Ratnayake, Raymond, Sanders, Spiers, Wetherell, Yiannakou Revised Investigator Data: Protocol 27018966IBS3001: Canaan, Fraser, Godwin, Guiterrez, Harlan, Harper, Heurich, Lillo, Mascaro, Movafagh, Sensenbrenner, Walker; Protocol 27018966IBS3002: Barreto, Hazan, James, Joshi, Kaner, Kelly, Kutner, Lefebvre, McLean, McNeil, Mikola, Morelli, Nichol, Olafsson, Poole, Sligh, Stewart, Strout, Thiwan
12/11/2012	USA	IND 79214	0089	Other	Request for Comment on proposed criteria for terminating dose group in carcinogenicity studies
12/12/2012	USA	IND 79214	0090	Protocol Amendment: Change in Protocol;#Response to Request for Information	Response to FDA's request for information (FDA letter dated 10 Oct 2012) regarding Phase 1 program. Revised protocol 27018966CPS1008 (Ver 1.0) (QTc study) based on FDA's comments in their letter dated 02 Nov 2012
12/20/2012	USA	IND 79214	N/A	Letter	FDA provides response to SN 0089 indicating that the early termination strategy was acceptable and that if the studies reached Week 100 and a dose group declined to 15 animals for any sex, all dose groups could be terminated
12/20/2012	USA	N/A	N/A	Letter;#Email	Furiex confirms USAN adoption of eluxadoline

1/8/2013	USA	IND 79214	0091	Protocol Amendment: New Investigator	New Investigator Information for Protocol 27018966CPS1005: Marbury, T; Protocol 27018966CPS1008: Hunt, T; 27018966IBS3001: Coulson W, Gooding T, Harbord M, Jackson A, Lee S, Rowlands S, Swindal HI, Thurston S; and Protocol 27018966IBS3002: Condon D, Griffin C, and Murphy M. Revised Invesigator Data for Protocol 27018966IBS3001: Aggarwal, Baber, Boagni, Cheung, Coppola, Culpepper, Desta, Florez, Godwin, Hardi, Hartvickson, Heurich, Hoekstra, Kelehan, Kim, Kimmel, Lodewick, Lorch, Mascaro, Movafagh, Petro, Pulver, Rhudy, Ricci, Slandzicki, Tarleton, Woyshville, Wukelic; Protocol 27018966IBS3002: Amas, Dewan, Hemaidan, Janovitz, Kaplan, Kutner, Lapham, MacGillivray, Nayyar, Pappas, Quader, Smith-Nguyen
1/16/2013	USA	IND 79214	0092	Safety Report: Initial	Initial Safety Report for 2013JJ000001 (Acute Drug Induced Hepatitis)
1/23/2013	USA	IND 79214	0093	Safety Report: Follow-up	Follow up safety report (1) for 2013JJ000001
1/28/2013	USA	IND 79214	0094	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator	Amendment 1 to Protocol 27018966CPS1008. New Investigator Information. Study 3001: Investigators Bodalia B, Bonner J and McAnsh G; Study 3002: Woods B. Revised Investigator Information for 3001: Apelsoff G, Block B, Cannon D, Clark L, Harlan W, Harris H, Jones M, Laurent A, Pang W, Riccio C, Shockey G, Tatum H, Teixeira G, Wo J; Study 3002: Alpizar S, Armas E, Farrell J, Jones J, Kearney K, Kozlov N, Lovell C, Mahmood K, McLean B, Michon A, Olivarez E, Samarasekera N, Saniuk R, Sauer M, Weinberg B, Wine A, and Wyatt D.
1/30/2013	USA	IND 79214	N/A	Letter;#Email	Letter to Office of Scientific Investigations concerning Dr. Pappas
2/5/2013	USA	IND 79214	0095	Safety Report: Follow-up	Follow up safety report (2) for 2013JJ000001
2/5/2013	USA	IND 79214	N/A	Letter	Letter to Office of Scientific Investigations concerning Dr. Elbanna
2/11/2013	USA	IND 79214	0096	General Correspondence	Notification of Breach in Protocols 27018966IBS3001 and 27018966IBS3002 concerning IVR misallocation of kits
2/13/2013	USA	IND 79214	N/A	Telephone Contact Report	FDA Requests location in IND of Elbanna CV and 1572.

2/13/2013	USA	IND 79214	N/A	Email	Furiex responds to FDA request made earlier the same day and provides location of Elbanna CV and 1572 in IND. FDA replies that they want all reports that have gone to OSI concerning investigator misconduct be submitted to the IND formally
2/14/2013	USA	IND 79214	0097	General Correspondence	Formal submissions to the IND of copies of the OSI reports for Drs. Elbanna and Pappas (27018966IBS3002) and Drs. Amann, Van Ginkel and Blumenthal (27018966IBS2001)
2/15/2013	USA	IND 79214	0098	DSUR	DSUR for reporting period of 21 Dec 2011 to 20 Dec 2012
2/19/2013	USA	IND 79214	0099	Protocol Amendment: New Protocol;#Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator	Protocol Amendment for 27018966CPS1005 (Amendment 2) New Protocol for 27018966CPS1009. 1572/CV for Hunt. TORO. New Protocol for 27018966CPS1011. 1572/CV for Medlock. TORO.
2/20/2013	USA	IND 79214	0100	Safety Report: Follow-up	Follow up (3) safety report for 2013JJ000001
2/27/2013	USA	IND 79214	0101	Protocol Amendment: Change in Protocol;#Protocol Amendment: New Investigator	Protocol Amendment 3 (Version 4) for 27018966CPS1005. Protocol Amendment for New Investigators: Study 3001: Jagarlamudi, McIlwain and Pandya; Study 3002: Grosman, Hasler, Kuo, Whorwell Protocol Amendment: Revised Investigator Information: Study 3001: Adams, Ainsworth, Barnes, Blagden, Brunskill, Cahill, Carr, Cheung, Coulson, Eavis, Essink, Falk, Gatof, Gooding, Hartvickson, Hellstern, Jackson, Jacobs, Kerrane, Koehler, Krumian, Menasha, Miller, Movafagh, Pfeifer, Rowlands. Study 3002: Acosta, Baum, Bowden, Call, Dar, Fisk, Henein, Holmes, James, Jones, Karnam, Kozlov, Lapham, MacGillivray, Mergener, Middleton, Mosley, Poole, Spiers, Sugantharaj, Wyatt
3/5/2013	USA	IND 79214	0102	Information Amendment: Pharmacology/Toxicology	Final study report for juvenile rat tox (study 1808-018)

3/20/2013	USA	IND 79214	0103	Protocol Amendment: New Investigator	New and Revised Investigator Data. Study 27018966IBS3001: New Investigators: Fernandez, Gowda, Harrington. Revised: Blagden, Corey, Coulson, Gaunt, Hellstern, Jr., Kemp, Marple, Murphy, Palatnik. Study 27018966IBS3002: New Investigators: Robinson, Williams. Revised: Armas, Bargar, Carpenter, Dar, Grudell, Holbrook, Kutner, Lumb, Maier, McLean, Middleton, Reynolds, Robison, Sauer, Sharpe, Stewart, Willette. Study 27018966CPS1008: Revised Investigator Data: Hunt.
3/20/2013	USA	IND 79214	N/A	Email;#Other	Correspondence between M. Usher and A. Davis (FDA) regarding submission content/format for the request of proprietary name review
4/16/2013	USA	IND 79214	0104	Other	Request for Proprietary Name Review: Xenryma
4/30/2013	USA	IND 79214	N/A	Email;#Other	Email correspondence (30 April - 03 May 2013) between M. Usher and A. Davis (FDA) regarding the timing of submission of the pediatric study plan in relation to the NDA submission and timing of pre-NDA meeting.
5/9/2013	USA	IND 79214	0105	Protocol Amendment: New Investigator	New and Revised Investigator Data. Study 27018966IBS3001. New: Broker, Butterworth, Paul, Spencer, Turner, Wright, Young. Revised: Canaan, Dryden, Jr., Gaspari, Huffman, Kessel, Poulos, Slandzicki, Sternlicht, Stollman, Thompson, Wyman. Study 27018966IBS3002. New: Barranco, Davidson, Florea, Nanda. Revised: Andersen, Azizad, Baxter, Butler, Farsad, Gentry, Herman, Hess, House, Kelly, Mattar, Pappas, Poindexter, Poindexter, Surowitz, Surowitz, Weinstock, Wine.
5/15/2013	USA	IND 79214	0106	Safety Report: Initial	Initial Safety Report. Study 27018966CPS1005. Mnf Cntrl No: 2013JJ0000049. Ileus.

5/16/2013	USA	IND 79214	N/A	Telephone Contact Report;#Other	Ms. Davis (FDA) called to reply to email correspondences regarding the timing of a request for a pre-NDA meeting with the GI division, considering the difficulty in scheduling meetings lately within the 60-day allowance. She agreed that a request could be submitted as early as 4 months prior to the meeting, containing prelim questions. Finalized questions will be due 2 months from the actual meeting date. We are to mention this agreement in the cover letter of the initial meeting request.
5/24/2013	USA	IND 79214	0107	Protocol Amendment: New Investigator	New Investigators Study 3001: Dimitroff, Godbole, Iduru, Jones, Kazi, Kutner, Velez; Study 3002: Parmar, Qadri, Tresser Revised Investigators Study 1007: Bradley; Study 3001: Alfonso, Benson, Cova, Dhillon, Focil, Kemp, Krumian, Moretti, Neuman, Patel, Seidner, Tatum, Thompson, Jr., Wagner, Young, Zachow; Study 3002: Andersen, Armas, Dobkin, Drummond, Essink, Felber, Grudell, Gunaratnam, Johnston, Karnam, Koval, MacGillivray, Mikola, Noar, Olden, Quader, Rall, Rauh, Sharpe, Spierings, Strout, Surowitz, Tang, Wilson
6/5/2013	USA	IND 79214	0108	Safety Report: Follow-up	IND Safety Report (FU1) for 2013JJ000049 (Ileus)
6/25/2013	USA	IND 79214	0109	Safety Report: Follow-up	IND Safety Report - Amendment to FU (1) for 2013JJ000049 (Ileus)
6/25/2013	USA	IND 79214	N/A	Letter;#Other	Notification to Office of Scientific Investigations for the Site Closure of J. Lassiter (Tiffin, Ohio) in Study 3002 due to his guilty plea of conspiracy to distribute controlled substances.

					New Investigators Study 3001: Acosta, Allaw, Alpizar, Aran-Serrano, Armas, Bargar, Barreto, Bassan, Behrend, Borders, Bowden, Brody, Clark, Collins, Cook, Dar, DeBusk, Diaz, Dobkin, Ericksen, Eweje, Farrell, Fernandez, Ferreira, Gaddam, Galvez, Gentry, Gold, Gorgi-Mikhail, Grande, Jr., Harrington, Hazan, Hemaidan, Holmes, Intelisano, Kaplan, Kelley, Klein, Lapham, Lee, Lefebvre, Lewy-Alterbaum, MacGillivray, Maynard, McNeil, Moussa, Moyer, Muller, Jr., Perez Limonte, Perwien, Pineda-Velez, Pratt, Raikhel, Samano, II, Saniuk, Seep, Shah, Sharpe, Siddiqui, Sligh, Souder, Spierings, Staffetti, Stewart, Strzinek, Suiter, Surowitz, Tang, Torres, Tripuraneni, Turner, Weinberg, Wiener, Zwick; Study 3002: Qadri Revised Investigators Study 3001: Almaguer, Ballinger, Brunskill, Cannon, Dhillon, DiGiovvanna, Dunn, Fairhead, Harlan, Hellstern, Jr., Heurich, Inadomi, Ingham, Jamal, Jones, Kamyar, Kessel, Langan, Levine, Levy, Jr., Limkermann, Phillips, Schmidt, Slandzicki, Spencer, Walker; Study 3002: Aboudsaif, Ahmad, Baxter, Bissette, Cha, Notification of Site Closure for J. Lassiter.Davidson, Fernandez, Fisk, Galvez, Ginzburg, Halwan, Holmes, Jones, Klein, Koser, Kuo, Kutner, Minkowitz, Munoz, Noar, Olusola, Ratnayake, Robison, Salazar, Schmidt, Stewart, Wallace, Wayne, Weinberg
7/2/2013	USA	IND 79214	0110	Protocol Amendment: New Investigator;#Information Amendment: Clinical;#Other	Post-hoc PK Analysis for Study 27018966IBS2001
7/19/2013	USA	IND 79214	0111	Letter;#Protocol Amendment: New Protocol;#Protocol Amendment: New Investigator;#Other	New protocol 27018966CPS1012 evaluating the effect of multiple doses of eluxadoline on the PK of a single dose of rosuvastatin. Provided 1572/CV for Dr. Hunt. Provided TORO for the study as well.

7/26/2013	USA	IND 79214	0112	Letter;#Protocol Amendment: New Investigator	New Investigator Data 3001: Patel; 3002: Madonado-garcia, Pharr Revised Investigator Data: 1007: Vince; 3001: Caldwell ,Cheung ,Collins ,Crespo ,Eavis ,Evans ,Fein ,Ferrera ,Galvez ,Harlan ,Huffman ,Koch ,Leggett ,Lodewick ,Paul ,Race ,Seep ,Spierings ,Wukelic; 3002: Davidson ,Farsad ,Ginzburg ,Goetsch ,House ,Intelisano ,Jones ,Kozlov ,Davidson ,Farsad ,Ginzburg ,Goetsch ,House ,Intelisano ,Jones ,Kozlov ,Lynd ,McElya ,Michael ,Mikola ,Minkowitz ,Minton ,Munoz ,Poole ,Rankin ,Rauh ,Raymond ,Robison ,Samarasekera ,Sauer ,Seep ,Spierings ,Varano ,Wetherell
7/31/2013	USA	IND 79214	0113	Letter;#Other	Type C meeting request to discuss pediatric study plan
8/2/2013	USA	IND 79214	N/A	Letter;#Email;#Other	Letter to Office of Scientific Investigations concerning a SubInvestigator (Dr. Rousseau) of Site #519 (Dr. Torres Site) for Study 3002 was indicted on charges to commit conspiracy of healthcare fraud.
8/7/2013	USA	IND 79214	0114	Letter;#Other	Type C meeting request to discuss adequacy of the abuse liability assessment performed to date
8/7/2013	USA	IND 79214	N/A	Letter;#Email	Letter to Office of Scientific Investigations concerning Study 3002 of two incidences of a site having access to another site's data. Corrective actions were provided.
8/9/2013	USA	IND 79214	0115	Letter;#Other	Copies of letters sent to Office of Scientific Investigations concerning the SubI (Rousseau) and EDC misallocation
8/9/2013	USA	IND 79214	N/A	Email;#Other	FDA grants Type C meeting on 15 October 2013 to discuss pediatric development program (SSN 0113) and requests mtg package and 15 desk copies by 17 September
8/14/2013	USA	IND 79214	N/A	Email;#Other	FDA Grants Type C meeting (written responses only) to discuss adequacy of abuse liability program (see SN 0014).

8/16/2013	USA	IND 79214	N/A	Email	Email communications that occurred between Ms. Davis (FDA) and Ms. Usher (Furiex) from 10 -16 August 2013 regarding the Type C meeting to discuss the PSP. Ms. Davis requested our preference for handling of the meeting minutes, and denoted a change in meeting time.
8/16/2013	USA	IND 79214	N/A	Letter	FDA Grants Type C meeting request (written responses only) with CSS to discuss the abuse liability program (refer to request submitted in SN 0114).
8/16/2013	USA	IND 79214	N/A	Email	Email correspondence between M. Usher and A. Davis regarding the change in time of the Type C meeting (Pediatric Development) on 15 October. Meeting is now from 9:30 to 10:30.
8/23/2013	USA	IND 79214	0116	Protocol Amendment: New Investigator	New Investigators: Study 27018966IBS3001: Cookson. Revised Investigators: Study 27018966CPS1005: Berg, Marbury. Study 27018966IBS3001: Allaw, Arora, Barish, Corey, Desta, Fernandez, Fruchter, Godbole, Gonte, Green, Kessel, Krumian, Kumar, Lapham, Laurent, Marilley, McLaughlin, Merrick, Peters, Seep, Shah, Sutter, Torres, Williams. Study 27018966IBS3002: Allaw, Davidson, Dewan, Essink, Fernandez, George, Kennedy, Lapham, Miner, Munoz, Oberoi, Poindexter, Seep, Souder, Stewart, Torres, Wayne.
8/27/2013	USA	IND 79214	N/A	Email;#Other	Email correspodnence between M. Usher and A. Davis regarding the date that the meeting package (and desk copies) for the Type C meeting (Pediatric development) is needed. FDA requests that the package be provided no later than 16 September 2013.
8/29/2013	USA	IND 79214	N/A	Email;#Other	Email correspondence between M. Usher and A. Davis regarding changing the time of the Type C meeting with CSS (human abuse liability program). The written responses will not be available on 06 December 2013 requiring Furiex to provide the meeting package no later than 06 November 2013.

9/3/2013	USA	IND 79214	0117	Letter;#Safety Report: Follow-up	Follow up (2) to IND Safety Report - 2013JJ000049 (Study 27018966CPS1005)
9/8/2013	USA	IND 79214	N/A	Email;#Other	Email correspondences between M. Usher and A. Davis defining how the references should be provided in the desk copies for the Type C meeting (Pediatric development). Refer to Mtg request in SN 0113. FDA indicates that due to the large volume of references, there is no need to provide these in the desk copies, but just denote where they can be found in the electronic submission.
9/9/2013	USA	IND 79214	0118	Letter;#Information Amendment: Pharmacology/Toxicology;#Information Amendment: Clinical	Nonclinical Information Amendment to include final study reports for Study 1808-019 (Seg III) and Study 100006176 (in vitro binding assays of JNJ-27018966-AAC) Clinical Information Amendment to include final Phase 1 study reports for Study 27018966CPS1008 (QTc); Study 27018966CPS1009 (Food effect); Study 27018966CPS1011 (MRP2)
9/13/2013	USA	IND 79214	0119	Letter;#Other	Type C Meeting Package to discuss the Pediatric Development (includes draft PSP). (also provided 15 desk copies)
9/13/2013	USA	IND 79214	N/A	Letter	FDA tentatively accepts the proprietary name of XENRYMA
9/24/2013	USA	IND 79214	0120	Protocol Amendment: New Investigator	New Investigator Information for Study 27018966IBS3001: Cullen, Eagerton, Gardner; Study 27018966IBS3002: Kravitz. Revised Investigator Information for Study 27018966IBS3001: Crespo, Gentry, Harris, Hartvickson, Jones, Karn, Kessler, Kutner, Lesh, Levy Jr., Lodewick, Maynard, Ojuri, Race, Raikhel, Schwarz, Stroud and Tatum; Study 27018966IBS3002: Barreto, DeMicco, George, Grant, Gunaratnam, House, Klein, Lembo, Maiki, Resnick, Strzinek, Surowitz and Tripuraneni.

9/26/2013	USA	IND 79214	N/A	Letter;#Email;#Other	OSI Notification of Site Closure of Silvera (Study IBS-3001) due to GCP compliance issues
9/30/2013	USA	IND 79214	0121	Letter;#Information Amendment: Clinical	Copy of Notification to OSI regarding the termination of Dr. Silvera site from participation in Protocol 27108966IBS3001.
10/4/2013	USA	IND 79214	0122	Information Amendment: Clinical	Version 3.2 of Final SAPs for Protocols 27018966IBS3001 and 27018966IBS3002
10/8/2013	USA	IND 79214	0123	Letter;#Other	Request for Comment on Furiex Approach of Documenting Lost to Follow-up Subjects in the Phase 3 trials 27018966IBS3001 and 27018966IBS3002
10/10/2013	USA	IND 79214	N/A	Letter	FDA's preliminary responses to Type C Meeting Request questions (SN 0113) regarding the pediatric development of eluxadoline
10/25/2013	USA	IND 79214	N/A	Letter	FDA provides final minutes from Pediatric Type C Meeting held on 10/15/2013 to discuss the pediatric development of eluxadoline
10/28/2013	USA	IND 79214	0124	Protocol Amendment: New Investigator	Revised Investigator Data for Study 27018966IBS3001: Ballinger, diGiovanna, Ericksen, Fairhead, Godbole, Harwitt, James, Jones, Kalafer, King, Lee, MacGillivray, Makam, Meisner, Palatnik, Paul, Scarsella, Stewart, Stollman, Surowitz, Sutter, Tomlinson, Turner and Wagner; Study 27018966IBS3002: Balakrishnan, Dobkin, Farrell, Ferreira, Foley, Jones, Lee, MacGillivray, Moses, Raijman, Randall, Salazar, Saniuk, Shah, Stern and Syed.
10/31/2013	USA	IND 79214	0125	Information Amendment: Clinical	Submission of Final Clinical Study Reports for Studies: 27018966CPS1005, 27018966CPS1007 and 27018966CPS1010.
11/5/2013	USA	IND 79214	0126	Other	Type C Meeting Package to support questions submitted on 07 August 2013 (serial submission 0114) concerning eluxadoline's abuse liability assessment to supporting an NDA submission.
11/10/2013	USA	IND 79214	N/A	Email	FDA indicates 27018966IBS3001/3002 Protocol SAPs (Version 3.2) are acceptable.

11/11/2013	USA	IND 79214	N/A	Email;#Other	FDA confirms status of their review of SN 0123 (submitted on 08 Oct 2013) regarding how to document attempts to address LTFU subjects in the Phase 3 studies. FDA expects to have responses by 17 Dec 2013.
11/14/2013	USA	IND 79214	0127	Other	Submission of Final Pediatic Study Plan including sponsor's version of meeting minutes (pediatric development) held on 15 October 2013 with FDA.
11/18/2013	USA	IND 79214	N/A	Email;#Other	As requested by FDA, Furiex provides a MS Word copy of the final PSP
11/19/2013	USA	IND 79214	N/A	Email;#Other	FDA provides agreement with the protocol SAPs for 27018966IBS3001/3002 submitted on 04 Oct 2013 (SN 0122)
11/25/2013	USA	IND 79214	0128	Other	Type C Meeting Request/Package requesting feedback on preliminary ISS/ISE SAPs
11/26/2013	USA	IND 79214	0129	Protocol Amendment: New Investigator	New Investigator Data Study 3001: Preston and Sanchez; Study 3002: Landor, Mann, and Yacyshyn Revised Investigator Data Study 3001: Alexander, Barish, Blagden, Blankfield.Gonte, Harwitt, Hejeebu, Heurich, Klein, Petro, Pulver, Schwender, and Zuckerman; Study 3002: Garner, Grosman, Kaplan, Klein, Maiki, Prince, Pudi, and Sedghi
11/26/2013	USA	IND 79214	N/A	Email;#Other	As requested by FDA, Furiex provides a MS Word copy of the questions submitted in SN 0128 (Type C Meeting - Written Responses only for comment on ISS/ISE SAPs)
11/27/2013	USA	IND 79214	N/A	Letter	FDA Grants a Type C Meeting (Written Responses only) to address ISS/ISE Questions
12/4/2013	USA	IND 79214	N/A	Email	FDA provides guidance on requirements for the pregnancy section of the label
12/4/2013	USA	IND 79214	N/A	Letter	Furiex notifies OSI of site closures of Drs Kessler (Study 27018966IBS3001), Michon, Ayub and Landor (Study 27018966IBS3002)

12/5/2013	USA	IND 79214	0130	Information Amendment: Clinical	Copy of OSI letter for closure of the following sites: Kessler (Study 27018966BS3001), Michon, Ayub and Landor (Study 27018966IBS3002)
12/6/2013	USA	IND 79214	N/A	Letter	FDA/CSS provides written responses to Type C Meeting Questions (see serial submission 0126)
12/8/2013	USA	IND 79214	N/A	Email	Email correspondences originating from M. Usher on 12/6/2013 after receipt of CSS Written responses requesting a telecon with the FDA to clarify their responses. FDA replies on 12/8/2013 with a possible meeting date/time.
12/9/2013	USA	IND 79214	N/A	Email	Email correspondences on 12/9/2013 between M. Usher (Furiex) and A. Davis (FDA) concerning meeting logistics for follow up conf call to be held on 12/10/2013 with FDA to discuss the FDA/CSS responses dated 12/6/2013.
12/10/2013	USA	IND 79214	N/A	Email	Email correspondences between M. Usher (Furiex) and A. Davis (FDA) regarding the cancellation of the 12/10/2013 meeting due to weather. FDA proposed to reschedule the meeting on 1/16/2014 at 1pm.
12/13/2013	USA	IND 79214	N/A	Email;#Other	Email correspondences confirming 19Dec2013 teleconference to discuss FDA/CSS tamperability/extractability comments in their 06Dec2013 letter
12/13/2013	USA	IND 79214	N/A	Letter;#Other	FDA accepts Furiex approaches to the handling of LTFU subjects in Phase 3 trials (see SN 0123)
12/15/2013	USA	IND 79214	N/A	Email	series of emails with FDA concerning the logistics of the 19 Dec 2013 teleconference and to obtain a face to face meeting on 16 Jan 2014 (discussing FDA/CSS responses in 06 Dec 2013)
12/16/2013	USA	IND 79214	0131	Protocol Amendment: Change in Protocol	Submission of Phase 3 Protocol Amendment 4 for 3001 and 3002
12/16/2013	USA	IND 79214	N/A	Email;#Other	FDA confirms 16 Jan 2014 face to face meeting with CSS to discuss the 06Dec2013 responses
12/17/2013	USA	IND 79214	N/A	Email;#Other	Furiex provides supplementary meeting materials for the 19 Dec 2013 teleconference

12/17/2013 USA	IND 79214	N/A	Letter;#Other	Furiex notifies OSI of the Closure of Dr. Sirakoff (3002 Study)
12/18/2013 USA	IND 79214	0132	Letter;#Other	Pre-NDA CMC Meeting Request
12/18/2013 USA	IND 79214	N/A	Email;#Other	FDA provides meeting attendees list for the 19 Dec 2013 teleconference.
12/20/2013 USA	IND 79214	N/A	Letter;#Email;#Other	Furiex notifies OSI of possible falsificati0n of data at Lewy-Alterbaum site (3001)
12/23/2013 USA	IND 79214	0133	Letter;#Other	OSI notification of Site Closure of Dr. Sirakoff (3002) and possible falsification of data at Dr. Lewy-Alterbaum (3001) site.
12/24/2013 USA	IND 79214	N/A	Email;#Other	FDA provides meeting attendees list for 16 Jan 2014 face to face meeting
12/26/2013 USA	IND 79214	0134	Letter;#Safety Report: Initial	IND Initial Safety Report 2013JJ000139 for erythema nodosum (in Study1006)
1/3/2014 USA	IND 79214	0135	Letter	Pre-NDA Clinical/General Meeting Request
1/7/2014 USA	IND 79214	0136	Letter;#Other	Furiex replys to FDA/CSS 06Dec2013 letter and provides supplementary information for the 16 Jan 2014 face to face meeting
1/7/2014 USA	IND 79214	N/A	Letter	FDA Grants Pre-NDA Meeting for 22 April 2014
1/8/2014 USA	IND 79214	N/A	Letter;#Other	FDA Grants Pre-NDA CMC Meeting for 25 Feb 2014 from 11:30 - 12:30.
1/9/2014 USA	IND 79214	0137	Letter;#Protocol Amendment: New Investigator	Revised Investigator Information for Phase 3 Studies. 3001: Gonte, Harlan, Kutner, Marilley, Rudolph, Salvato, Thompson; 3002: Gentry, Gordon, Janovitz, Martin, Muller, Murphy, Rinesmith, Satterfield
1/9/2014 USA	IND 79214	N/A	Email;#Other	FDA is planning on canceling the 16 Jan 2014 meeting as no new information/questions were provided (seen SN 0136) and will provide written responses instead
1/10/2014 USA	IND 79214	0138	Safety Report: Follow-up	Follow-up (1) Safety Report for 2013JJ000139 (Study 1006)
1/10/2014 USA	IND 79214	N/A	Letter;#Other	FDA canceled the 16 Jan 2014 meeting as no new information/questions were provided (seen SN 0136) and will provide written responses instead

1/18/2014	USA	IND 79214	N/A	Letter;#Other	FDA/CSS provides follow-up responses from 06 Dec 2013 letter and Furiex's SN 0136 submission regarding the eluxadoline human abuse liability program
1/23/2014	USA	IND 79214	0139	Other	Pre-NDA CMC Mtg Pkg
1/23/2014	USA	IND 79214	N/A	Email	As requested by OSI (D. Walters by phone) Furiex provides additional information to OSI concerning the Phase 3 site closures in their 04 Dec 2013 letter
1/31/2014	USA	IND 79214	0140	Letter;#Protocol Amendment: New Investigator	New Investigator Data: Study 3001: Bramlet; Study 3002: Ali Revised Investigator Data: Study 3001: Arora, Arslanian, Bekal, Dhillon, Eagerton, Gonzalez, Harper, Infusino, Kemp, Kutner, Schwarz, Shockey, Walker; Study 3002: DeMicco, Farsad, Horwitz, Kaufmann, Kutner, O'Barr, Sargeant, Tessler
1/31/2014	USA	IND 79214	N/A	Letter	FDA corrects DIBD date from earlier correspondence.
1/31/2014	USA	IND 79214		Letter	FDA provides written responses to Type C meeting request regarding ISS/ISE plans (serial submission 0128).
2/3/2014	USA	IND 79214	N/A	Letter	FDA provides feedback on initial PSP submission (see serial submission 0127).
2/5/2014	USA	IND 79214	0141	Information Amendment: Pharmacology/Toxicology;#Information Amendment: Clinical;#DSUR	Submission of DSUR-03. Nonclinical Information Amendments for Carc Reports (1808-008 and 1808-009) and Phototox report (2004699); Clinical Information Amendment: IB Edition 9, Final CSR for 28018966CPS1012 and Errata to 27018966IBS2001 CSR
2/6/2014	USA	IND 79214	0142	Letter;#Safety Report: Follow-up	Follow up Safety Report (2); 2013JJ000139FU2
2/6/2014	USA	IND 79214	N/A	Email;#Other	FDA assigns the pending NDA number of 206,940 to eluxadoline.
2/7/2014	USA	IND 79214	N/A	Letter;#Other	User Fee Waiver Request for Small Business
2/14/2014	USA	IND 79214	N/A	Letter;#Other	FDA provides preliminary feedback on Pre-NDA CMC Meeting Questions (serial submission 0132)

2/17/2014	USA	IND 79214	N/A	Email;#Other	Furiex requests clarifications on preliminary comments received from FDA (dated 14 Feb 2014) concerning the preNDA CMC meeting
2/20/2014	USA	IND 79214	0143	Letter;#Other	Revised Questions for Pre-NDA Meeting
2/24/2014	USA	IND 79214	N/A	Email	FDA replies to Furiex's email of 2/17/2014 providing further clarification that it is acceptable to submit the NDA with 6months of API stability data in the Marvelseal bags and that the NDA can be amended with updated stability data 30 days after NDA submission.
2/24/2014	USA	IND 79214	N/A	Email;#Other	Furiex cancels the Pre-NDA CMC teleconference in light of FDA responses received on 14 Feb and 24 Feb 2014 and requests that the meeting responses including the email communication received on 24 Feb be provided formally in writing to Furiex for their records
2/26/2014	USA	IND 79214	0144	Letter;#Protocol Amendment: New Investigator	New Investigator Data for Study 3001: Jarrett, Kaine Revised Investigatory Data for Study 3001 Revised: Alfonso, Canaan, Dryden, Kalafer, Kastelic, Kemp, Lewy-Alterbaum, Lodewick, Mascaro, Pulver, Scarsella, Schey; Revised Data for Study 3002: Armas, Dorn, Drummond, Lacy, Moussa, Olivarez, Sedghi, Tessler
2/26/2014	USA	IND 79214	N/A	Email	FDA Nonclinical Information Request: requests Tumor Carc Datasets from Studies 1808-008 and 1808-009 submitted on 2/5/2014 (Serial Submission 0141)
2/28/2014	USA	IND 79214	N/A	Email	FDA agrees that the preNDA meeting package can be submitted electronically on 21 March 2014 (with desk copies received on 24 March 2014)
3/3/2014	USA	IND 79214	0145	Letter;#Response to Request for Information	Furiex provides Tumor datasets for Studies 1808-008 and 1808-009
3/6/2014	USA	IND 79214	0146	Other	Response to FDA comments on iPSP
3/6/2014	USA	IND 79214	N/A	Email	FDA confirms receipt of receipt of serial submission 0146 and the MS Word version of the revised iPSP containing Furiex's responses to FDA letter dated 2/23/2014

3/21/2014 USA	IND 79214	0147	Letter;#Other	PreNDA Meeting Package
3/21/2014 USA	IND 79214	N/A	Email;#Other	Email communication of 3/20 - 3/21/2014 regarding finalizing iPSP
3/24/2014 USA	IND 79214	N/A	Letter;#Other	FDA provides response to follow-up to preNDA CMC preliminary responses. Refer to Furiex communication dated 17 February 2014 regarding API stabiliity data at time of NDA submission.
3/24/2014 USA	IND 79214	N/A	Email;#Other	Email communication about final agreed iPSP and timing for formal submission
3/24/2014 USA	IND 79214	N/A	Email;#Other	FDA clarifies the placement of the agreed upon iPSP in Module 1 of the pending eluxadoline NDA.
3/24/2014 USA	IND 79214	N/A	Email;#Other	FDA email confirming that the formal submission of the agreed upon iPSP can be made on 26 March 2014
3/26/2014 USA	IND 79214	0148	Letter;#Other	Submission of final agreed iPSP
3/27/2014 USA	IND 79214	0149	Letter;#Protocol Amendment: New Investigator	Revised Investigator Data for Study 3001: Arslanian, Dhillon, Ferrera, Godbole, Kemp, Kumar, Pulver, Reddy, Riccio, Thomas, Tripuraneni, Varunok; Study 3002: Grant, Henein, Maynard, Raikhel, Torres
3/28/2014 USA	IND 79214	N/A	Email;#Other	FDA provides preliminary feedback on label (package insert) format only.
4/1/2014 USA	IND 79214	N/A	Letter;#Other	FDA provides final agreement on iPSP.
4/14/2014 USA	IND 79214	N/A	Email	FDA provides plans for providing preliminary responses to preNDA meeting questions and provides followup feedback regarding label content
4/17/2014 USA	IND 79214	N/A	Email;#Other	Furiex attempts to clarify two responses provided in the PreNDA meeting responses (dated 17 Aoril 2014) regarding the timing of the renal study and the submission of the long-term safety data from Study IBS-3001
4/17/2014 USA	IND 79214	N/A	Letter;#Other	FDA provides preliminary responses of PreNDA meeting questions
4/18/2014 USA	IND 79214	N/A	Email;#Other	FDA indicates that they will respond to Furiex requests for clarification at the PreNDA meeting on 22 April 2014 (see clarification request sent to Agency on 17 April 2014)

4/22/2014	USA	IND 79214	N/A	Email;#Other	FDA provides names of FDA meeting attendees from PreNDA meeting of 22 April 2014
4/24/2014	USA	IND 79214	0150	Letter;#Other	Sponsor's version of PreNDA meeting minutes
4/24/2014	USA	IND 79214	N/A	Email;#Other	Furiex provides by email the meeting minutes from PreNDA meeting and an additional clarification question regarding submission options for the long-term safety data for Study IBS-3001. Formal submisison of meeting minutes will follow on 25 April 2014.
5/2/2014	USA	IND 79214	0151	Letter;#Protocol Amendment: New Investigator	Updated investigator information. New investigators for Study IBS-3001: Assouline-Dayan, Hart and Velasco. Revised Investigator Data for IBS-3001: Kelehan, Lee, Lentz, Mahood, Miranda, Moulton, Moyer, Patel, Reina, Sanchez. Revised Investigator Data for IBS-3002: Drummond, Farris, McKnight, and Raikhel
5/2/2014	USA	IND 79214	N/A	Letter	FDA's Version of PreNDA Meeting Minutes
5/2/2014	USA	IND 79214	N/A	Letter	Small Business Association deems Furiex to not meet the definition of a small business allowing the waiver of NDA user fees
5/4/2014	USA	IND 79214	N/A	Letter	FDA request for User Fee Contact Information
5/6/2014	USA	IND 79214	N/A	Email	Confirmation from FDA that no NDC number is needed to file NDA
5/7/2014	USA	IND 79214	N/A	Email	FDA Provides clarification to certain components of the PreNDA meeting and confirms that the safety update for the additional safety data from Study 3001 will only be to the text and tables of the ISS.

5/28/2014	USA	IND 79214	0152	Letter;#Protocol Amendment: New Investigator	Revised Investigator Data for IBS-3001: Armas, Carrigan, Claassen, Collins, DeSantis, DiSarli, Godbole, Jackson, Joyce, McGill, Poulos and Sternlicht. Revised Investigator Data for IBS-3002: Cohen, Miner and Sligh
6/2/2014	USA	IND 79214	N/A	Email	FDA has assigned two backup RPMs to our IND/NDA while Ms. Anissa Davis-Williams is on maternity leave. CDR Stacy Barley 301-796-2137 Stacy.Barley@fda.hhs.gov LCDR Jennifer Sarchet 240-402-4275 Jennifer.Sarchet@fda.hhs.gov
6/2/2014	USA	IND 79214	N/A	Email	Correspondence between Furiex (M.Usher) FDA (A. Davis-Williams) and ECG Warehouse (Jim Riley) about correcting the NDA number that the ECG Warehouse had on file for the ECG datasets
6/3/2014	USA	IND 79214	N/A	Email	Furix provides User Fee Contact Information in response to FDA letter dated 04 May 2014
7/9/2014	USA	IND 79214	N/A	Letter;#Other	FDA denies request for waiver of user fees indicating that Furiex is not a small business entity

7/10/2014	USA	IND 79214	0153	Letter;#Protocol Amendment: New Investigator	New and Updated Investigator Information for Study IBS-3001. New investigator data: Kuohung V. Revised investigator data: Acosta, Alfonso, Alpizar, Arora, Baber, Baird, Borders, Chappel, DiSarli, Dunn, Epstein, Figueroa, Godsell, Harper, Hendrix, Kessel, Kim, Lomboy, Makam, Moretti, Rubino, Tidman and Wo.
8/5/2014	USA	IND 79214	0154	Letter;#Protocol Amendment: New Investigator	Study IBS-3001: Updated Investigator Data for the following investigators: Acosta, Arslanian, Block, Boagni, Claassen, Ferrera, Gonte, Johnson, Kelehan, Klein, Moulton, Navayogarajah, Petro, Scowcroft, Velez, and Wo
8/28/2014	USA	IND 79214	0155	Letter;#Protocol Amendment: New Investigator	Study IBS-3001: Updated investigator information for the following investigator : Claassen, DiSarli, Finneran, Gentry, Iduru, Kimmel, Lorch, Miranda, Navayogarajah, Tripuraneni, and Weinstein
9/19/2014	USA	IND 79214	0156	Letter;#Protocol Amendment: New Investigator	Study IBS-3001: Updated Investigator Data for the following investigators: Aran-Serrano, Baber, Barish, Finneran, Hardi, Holmes, Iduru, Johnson, Klein, Levy, Lewy-Alterbaum, and Makam
10/30/2014	USA	IND 79214	0157	Letter;#Protocol Amendment: New Investigator	Updated Investigator Information for Study IBS-3001: Swauger
11/6/2014	USA	IND 79214	0158	Letter;#Other	Copy of OSI Notification concerning Investigator Kessel in Study IBS-3001
2/12/2015	USA	IND 79214	0159	Letter;#Information Amendment: Pharmacology/Toxicology;#Information Amendment: Clinical;#DSUR	DSUR-04; Submission of Nonclinical diastereomer reports of 1808-020, 1808-021; Submission of clinical study reports for CPS-1006, IBS-3001 and IBS-3002.

Exhibit 11

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26 June 2014

Donna Griebel, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **Submission of Original New Drug Application (NDA 206940) for XENRYMA™ (eluxadoline) Tablets**
REQUEST FOR PRIORITY REVIEW
REQUEST FOR PROPRIETARY NAME REVIEW

Dear Dr. Griebel:

In accordance with Section 505(v) of the Federal Food, Drug, and Cosmetic Act, and with the provisions of 21 CFR 314.50, Furiex Pharmaceuticals, Inc. (Furiex) is submitting an original New Drug Application (NDA 206940) for XENRYMA™ (eluxadoline) tablets indicated for the treatment of pain and diarrhea associated with diarrhea-predominant Irritable Bowel Syndrome (IBS-d).

As a result of receiving Fast Track Designation on 19 January 2011 for the eluxadoline development program, Furiex believes that this NDA would be eligible for Priority Review considering the seriousness of IBS-d, specifically its impact on the day-to-day functioning of the patient. Additionally once approved, XENRYMA will provide a significant improvement over existing treatment options for IBS-d, especially for male patients for which there is no approved therapy. Therefore, Furiex respectfully requests that this NDA receive a Priority Review classification.

Reference is made to our online communication dated 02 June 2014 to the U.S. Food and Drug Administration (FDA), regarding the FDA User Fee for XENRYMA (eluxadoline) – New Drug Application, User Fee ID Number PD3014275. A copy of the User Fee Cover Sheet, Form FDA 3397, and confirmation of wiring payment are enclosed in Module 1.1.3.

The proposed proprietary name of XENRYMA was conditionally accepted by FDA based on their correspondence dated 13 September 2013. None of the product characteristics have changed since the submission of the initial proprietary name review request; however, we are re-submitting the proprietary name request for completeness.

As required under 21 CFR 315.50, this NDA contains complete safety and efficacy data generated from the nonclinical and clinical eluxadoline development program previously discussed with the FDA and is consistent with agreements made at the 22 April 2014 Pre-

NDA meeting (see PreNDA meeting minutes dated 02 May 2014 and follow-up clarification communication dated 07 May 2014). Recall that our Phase 3 studies were designed to meet both FDA and EMA requirements; therefore this NDA contains efficacy data for both 3 months and 6 months of treatment using the composite endpoint of improvement in stool consistency and pain. Also, as agreed with the Agency and further documented in the above referenced meeting minutes, Furiex plans to amend the NDA shortly after the completion of Study IBS-3001 for additional long-term safety with an amended ISS including associated tables and figures, and labeling (if required) only. The initial NDA submission already contains the required long-term safety exposures meeting ICH and FDA recommendations.

We acknowledge FDA's agreements as documented in the PreNDA meeting minutes noted above as well as Chemistry agreements documented in correspondence dated 24 March 2014 that allow the submission of updated stability data of the active pharmaceutical ingredient within 30 days of the original NDA submission. Further agreements and impacted NDA submission components are described below.

- Draft container and carton label artwork with final trade-dress will be submitted within 60 days of the NDA submission; however, we have included draft labeling without final trade-dress in this original NDA submission. Please note that although we are seeking approval for the 100 mg strength only, we are supplying bottle/blister carton labeling for both the 75 mg and 100 mg strengths for completeness as both strengths were demonstrated to be efficacious.

  In addition to the bottle/blister labels, we have enclosed the draft and annotated labeling (denoting the 100 mg strength only) including a proposed Medication Guide. Please note that complete annotations are provided for the full prescribing information (FPI) only since the Medication Guide contains restatements of the warnings/precautions in the fully annotated FPI.

- A comprehensive 8-factor analysis including the recommendation for the *non-scheduling* of eluxadoline is contained in Module 1.11.4, as agreed upon and documented in the PreNDA meeting minutes. Our proposal for non-scheduling is based on extensive in vitro testing as well as the results from nonclinical studies and two human abuse liability studies. Additionally our non-scheduling rationale is based on data from the Phase 3 studies in IBS-d patients including: a) absence of adverse event data suggestive of abuse potential collected from the long-term treatment with eluxadoline and b) the absence of withdrawal from eluxadoline as demonstrated by the subjective opiate withdrawal scale.

- This NDA includes safety narratives for all deaths, serious adverse events, and certain other significant adverse events (AEs). Their content (including the identification of those significant AEs of interest to FDA) and location within the NDA are consistent with agreements documented in the PreNDA meeting minutes.

- As agreed to in correspondence dated 31 January 2014 and re-confirmed at the Pre-NDA meeting, this NDA contains the complete patient profiles in lieu of the case report forms (CRFs) for each patient that died, or who did not complete the study due to an adverse event from our Phase 2 and Phase 3 studies. However, for our Phase 1 studies, CRFs (or patient profiles) are supplied for those subjects meeting the specified criteria. Additionally, we have included additional patient profiles for specific adverse events of interest in compliance with agreements documented in the PreNDA meeting minutes.

- This NDA includes case report tabulations for all clinical studies, consisting of the datasets, the programming code for each analysis dataset and efficacy tables (i.e., Phase 2 and Phase 3 studies and ISE), data definition tables and the annotated CRFs (annotated CRFs for Phase 1 studies are not provided), consistent with agreements made during the PreNDA meeting. These SAS data sets exist in ADaM 2.0 under ADaMIG 1.0 and SDTM v1.2, under SDTM-IG 3.1.2 and their platform was deemed acceptable to the FDA based on the PreNDA meeting minutes. Please note that, as requested by the Agency, due to their large size, some datasets had to be split to meet the <1GB requirement.

- Further, to comply with the Office of Scientific Investigations (OSI) request for clinical study/site related information, Furiex has supplied the site data listings for both Phase 3 studies in the relevant study folders in Module 5.3.5.1 while the site datasets are located in Module 5.3.5.4 per your technical instructions (Attachment 1) in the PreNDA meeting minutes.

  A comprehensive list of all manufacturing facilities involved with the production of eluxadoline and/or XENRYMA is enclosed with this submission.

- Also, as noted in the PreNDA meeting minutes, FDA did not believe that a formal Risk Evaluation and Mitigation Strategy (REMS) was required. As such, this NDA does not contain a formal REMS but rather includes our plans for minimizing risks and their management post approval (see Risk Minimization Strategy in Module 1.16).

- Consistent with FDA's request, as a supplement to the Summary of Clinical Pharmacology section in the NDA, we have included in Module 2.7.2 the responses to the Question-Based Summary (Clinical Pharmacology Summary Aid).

Furiex confirms that we have uploaded the ECG waveforms collected from our Phase 1 QTc study (27018966CPS1008) to the ECG warehouse (ECG Upload ID 0130722105809a). Please see the enclosed ECG Warehouse Study Import Report.

Also, please note that as per FDA's communication dated 01 April 2014, Furiex reached agreement with the FDA on the initial pediatric study plan (iPSP). This iPSP is located in

Module 1.9 of this NDA along with the requests for pediatric deferral and waiver of age groups <6 year of age.

As noted above, this NDA is in full compliance with 21 CFR 314.50 and is provided electronically following the relevant ICH M4 and FDA guidances for electronic common technical document (eCTD) submissions. Signed originals from Section 31 from the form FDA 356h and the cover letter will be retained on file with Furiex Pharmaceuticals. Furiex is not submitting a separate field copy, but is notifying the field office of the submission of this electronic NDA. A copy of this notification is attached.

Lastly, Furiex would like to thank the FDA for their helpful guidance during the development of eluxadoline and look forward to continued interactions as the review of this application proceeds. Should you have any questions regarding this submission, please do not hesitate to contact Ms. Michelle Usher, Executive Director of Regulatory Affairs at Furiex Pharmaceuticals, Inc. She can be reached by phone at 919.456.7817 (office) or 919.818.7565 (cellphone), by facsimile at 919.456.7850, or by email at michelle.usher@furiex.com.

We would also like to take the opportunity to alert FDA that on 28 April 2014, Forest Laboratories, Inc., entered into a definitive agreement to acquire Furiex Pharmaceuticals, Inc. This acquisition has already received customary regulatory approval and is scheduled to be approved by the Furiex shareholders on 01 July 2014. Therefore, the merger is likely to be completed on 02 July 2014. We will continue to update the FDA regarding the acquisition and alert you of any changes impacting this NDA.

Furiex Pharmaceuticals Inc. considers the information in this submission to be confidential, proprietary, and trade secret and therefore protected from disclosure under the provisions of the Freedom of Information Act (5 U.S.C. 552(b)(4)) and FDA regulations of 21 CFR 20.61 and 314.430 (a) and (d). Should the Agency deem it appropriate to disclose any information in this submission to the public, please consult with the Furiex contact listed above prior to disclosure.

This submission has been electronically prepared by Aptiv Solutions. For technical questions regarding this submission, please contact Mehri Hezari-Adam at Aptiv Solutions, by phone at 919.228.4461, by facsimile at 919.226.1441 or email at mehri.hezari-adam@aptivsolutions.com. The eCTD submission was generated using Lorenz docuBridge, Version 5.4. The submission has been scanned for viruses using Kaspersky Endpoint Security 10 for Windows 10.2.1.23.

Sincerely,

Paul S Covington

Paul S. Covington, MD
Senior Vice President, Clinical Development and Operations
Furiex Pharmaceuticals, Inc.

Exhibit 12

NDA 206940 REGULATORY SUBMISSION AND CORRESPONDENCE CHRONOLOGY LOG

Furiex Pharmaceuticals, Inc.
Eluxadoline

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
26-Jun-2014	0000	Submission		Original NDA
11-Jul-2014	N/A	Correspondence - Letter		FDA acknowledges receipt of NDA for 27 June 2014
18-Jul-2014	0001	Submission Amendment - Patent Information, CMC, Field Copy Certification		New Patent Information for Patent 8,772,325 ; Revised Patent Information for Patent 8,344,011; Updated stability data for drug substance (9-month data in Marvelseal bags, 12-month data in Mylar bags)
30-Jul-2014	N/A	Correspondence - Email		Ms. Sarchet (FDA) denotes filing meeting scheduled for Week of 11 Aug 2014
8-Aug-2014	N/A	Correspondence - Email	FDA Request #1	FDA Information Request #1 - Clin Pharm Request for Information: (1) Bioanalytical method validation reports; (2) Address DDI with gastric acid reducers; (3) Provide POPPK datasets for IBS-2001; (4) corresponding dose for both the concentration time profile dataset and PK parameter dataset; (5) evidence of biliary elimination; (6) in vivo potential interaction of eluxadoline with BSEP transport; (7) re-format of PK datasets to assist in analysis. FDA requests response to Items 1-2 by 12 August and Items 3-7 by 22 August 2014.
8-Aug-2014	N/A	Correspondence - Email		Furiex confirms receipt of FDA Information Request #1
11-Aug-2014	N/A	Correspondence - Email	FDA Request #2	FDA Information Request #2 : IBS-3001 & IBS-3002 e-Diary Data Flow Diagram and IVR/IWR Vendor information
11-Aug-2014	N/A	Correspondence - Email		Furiex requests extension for response to Question #7 in Information Request #1 (reformatted PK/PD datasets) for 29 August 2014.
12-Aug-2014	0002	Submission - Response to Request for Information (#1)		Response to FDA Information Request #1 email dated 08 Aug 2014 (Items 1 and 2)
13-Aug-2014	N/A	Correspondence - Email		FDA Grants Furiex request for an extension to provide a response for Question 7 (IR #1) to 29 Aug 2014 (see request 11 Aug 2014)
13-Aug-2014	N/A	Correspondence - Email		FDA Requests Response for Information Request #2 by 25 Aug 2014
15-Aug-2014	0003	Submission - Response to Request for Information (#2)		Response to FDA Request #2 (IBS-3001 & IBS-3002 e-Diary Data Flow Diagram and IVR/IWR Vendor information)

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
19-Aug-2014	0004	Submission - Amendment for Draft Labeling		Submission of final draft labels with final trade-dress as committed to in the Pre-NDA Meeting
19-Aug-2014	N/A	Correspondence - Letter	FDA Request #3	FDA Request #3: Request for Methods Validation Materials to be sent to St Louis, MO labs
20-Aug-2014	N/A	Correspondence - Email		Email correspondences between Furiex and FDA regarding sending the methods validation materials
22-Aug-2014	0005	Submission - Response to Request for Information (#1)		Response to Request #1 (Items 3-6): Providing POP PK datasets for IBS-2001; location of dose information in EDI-1001 datasets;, location in NDA providing evidence of biliary elimination; and BSEP rationale
26-Aug-2014	N/A	Correspondence - Letter (Irix) - Response to FDA Request		Response to FDA Request #3: Irix provides method validation samples
26-Aug-2014	N/A	Correspondence - Letter (Patheon) - Response to FDA Request		Response to FDA Request #3: Patheon provides method validation samples
27-Aug-2014	N/A	Correspondence - Letter		NDA accepted for filing and receives priority review designation
28-Aug-2014	N/A	Correspondence - Letter		FDA acknowledges receipt of method validation materials (FDA Request #3)
29-Aug-2014	0006	Submission - Response to Request for Information (#1)		Response to FDA Request #1 (Item 7): Submission of reformatted PK/PD datasets. Provided revised AdAM datasets for EDI1002 (provides unique keys for fast/fed arms)
5-Sep-2014	N/A	Correspondence - Letter		FDA approves the proprietary name of "XENRYMA"
8-Sep-2014	N/A	Correspondence - Email		Email to Ms. Sarchet (FDA) requesting status of the Day 74 letter
9-Sep-2014	N/A	Correspondence - Phone Contact Report		Two voice-mail messages were left with Ms. Sarchet requesting status of the Day 74 letter.
10-Sep-2014	N/A	Correspondence - Email		Email to Brian Strongin (Chief Project Management staff) asking status of Day 74 letter.

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
10-Sep-2014	N/A	Correspondence - Letter	FDA Request #4	Day 74 Letter dated 09 Sep 2014 provided by email from J. Sarchet; FDA Request for Information: (1) Safety amendment: ISS, ISS datasets, 3001 CSR, label; (2) MeDRA hierarchy (3001, 3002 and for updated ISS datasets); (3) Electronic dissolution data; (4) Comparative dissolution data between debossed (registration batches) and non-debossed tablets (P3 batches); (5) Rationale for no REMs despite communication plan proposed; (6) Labeling comments. Letter was incomplete and did not provide the labeling comments as noted in the cover letter.
10-Sep-2014	N/A	Correspondence - Email		Furiex asks about the lack of labeling comments referenced in the Day 74 letter, and plans for the midcyle communication and Advisory Committee meeting. FDA denotes they will check into the problem.
10-Sep-2014	N/A	Correspondence - Email		FDA notes a problem with the format of the Day 74 letter (received earlier that day) and will be issuing another letter on 11 Sep 2014
11-Sep-2014	N/A	Correspondence - Email	FDA Request #5	FDA Request for Information: (1) Further delineation of pt dc for all "Physician decision: other" by study/by tx arm; (2) Tabulation of all protocol violations by study and violation; and (3) Updated subject disposition table (Enrolled set) for Study 3001. Deadline for response is 25 Sep 2014.
11-Sep-2014	N/A	Correspondence - Email		Furiex clarifies the contents of the pending revised Day 74 letter. FDA confirms that it will answer earlier questions about midcycle meeting and Advisory Committee plans. Furiex later requests status of the revised letter. Ms. Sarchet indicates that it is on Dr. Griebel's desk for signature and should be available shortly.
12-Sep-2014	N/A	Correspondence - Email		Furiex requests status of final Day 74 letter and an extension for the submission of the revised label (based on the delay in receipt of the final letter and that the label will be provided with the upcoming safety amendment).

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
12-Sep-2014	N/A	Correspondence - Email and Letter	FDA Revised Request #4	FDA provides by email their revised Day 74 letter containing the labeling comments. Letter is dated 09 September 2014 and states that there are currently no plans for Advisory Committee meeting and their internal midcycle communication meeting is planned for 04 December 2014.
17-Sep-2014	N/A	Correspondence - Phone Contact Report		Furiex requests that the revised label (see FDA Revised Request #4) be supplied with the safety amendment (no later than 27 October) and be provided in Word format only.
18-Sep-2014	N/A	Correspondence - Phone Contact Report		FDA agrees that label amendment (see FDA Revised Request #4) can be supplied with the safety amendment and that Word format is acceptable.
18-Sep-2014	N/A	Correspondence - Email		FDA confirms by email acceptance of submission strategy of label amendment
19-Sep-2014	N/A	Correspondence - Email		Email correspondences between Furiex and FDA (from 18 Sep to 19 Sep 2014) regarding the submission of the Excel spreadsheet containing dissolution data (requested in FDA Request #4). FDA agrees data can be supplied by email. On 19 Sep 2014 Furiex provides the electronic Excel spreadsheet containing dissolution data requested.
22-Sep-2014	007	Submission - Response to Information Request #4 and #5		Responses to Request #4: MeDRA hierarchy (3001, 3002 and for updated ISS datasets) and rationale additional risk measures proposed. Submission also contains responses to Request #5: Further delineation of pt dc for all "Physician decision: other" by study/by tx arm and tabulation of all protocol violations by study and violation. All other pending items will be supplied in upcoming safety amendment.
23-Sep-2014	N/A	Correspondence - Email	FDA Request #6	Email correspondence from Ms. Sarchet requesting a subject map file to match USUBJID in clinical datasets with those Subject ID in ECG Warehouse for Study CPS-1008.
24-Sep-2014	N/A	Correspondence - Email		Furiex provides by email the subject map file in Excel format (Response to FDA Request #6) and asks if the data needs to be formally submitted to the NDA in xpt

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26-Sep-2014	N/A	Correspondence - Email		FDA responds to Furiex email of 24 Sep indicating that the response to FDA Request #6 supplied by email is adequate and that no additional information is needed
8-Oct-2014	NA	Correspondence - Phone Contact Report		Ms. Sarchet (FDA) calls to request status of safety amendment; Agrees to the strategy for the submission proposed revised wording for indication statement in the labeling revisions being supplied in the safety amendment; Denotes an internal meeting with review team on 09 October 2014; Requests a copy of the cover letter for Seq 0008 in advance of the submission so that she can discuss it with her team at the meeting.
8-Oct-2014	NA	Correspondence - Email		Ms. Usher supplies a copy of the cover letter for the BIMO Amendment (seq 0008) in advance of the submission
9-Oct-2014	0008	Submission - Amendment to BIMO Listings/Dataset		BIMO listings/dataset were updated for the completion of IBS-3001 and to correct two errors in the earlier listings: diary data for non-responders and correct # protocol violations in listings
9-Oct-2014	NA	Correspondence - Email	FDA Request #7	Email correspondence from Ms. Sarchet requesting detailed explanation about how we determined various patients' composite response status using their raw data at each visit
16-Oct-2014	N/A	Correspondence - Email		Email correspondence to Ms. Sarchet providing a copy of Seq 0009 by email in advance of its submission to the NDA as requested
17-Oct-2014	0009	Submission - Response to FDA Request #7		Furiex provides explanation for responder status as requested by FDA in their 09 Oct 2014 email
23-Oct-2014	N/A	Correspondence - Email	FDA Request #8	FDA requests additional API and reference standard to perform KF testing
24-Oct-2014	0010	Submission - 120 Safety Update		120 Safety update includes 3001 amended CSR, supplement for 3001 CSR, ISS update, labeling, revised listing for 3002
28-Oct-2014	N/A	Correspondence - Email		Response to FDA Request #8: Furiex notes that API vendor shipped materials for overnight delivery
30-Oct-2014	N/A	Phone Contact Report		Furiex confirms FDA receipt of 120-day safety update and requests information on inspection status

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12-Nov-2014	N/A	Correspondence - Email		FDA says District office will be in touch shortly regarding inspections; DSUR can not be waived despite the recent safety amendment
21-Nov-2014	N/A	Correspondence - Email	FDA Request #9	PDUFA extension letter due to safety amendment. Also RFI for labeling revisions.
25-Nov-2014	N/A	Correspondence - Email	FDA Request #10	FDA Requests exposure breakdown for 75mg, 100 mg, and pbo for pooled P2&P3 studies
28-Nov-2014	N/A	Correspondence - Email		Email correspondences between M.Usher and J.Sarchet regarding midcycle communication meeting logistics
1-Dec-2014	N/A	Correspondence - Email	FDA Request #11	Requests info on viability of test systems used to assess metabolism of eluxadoline; metabolic profiling in fecal samples; sensitivity of metabolic profiling analysis; data to support human BA
1-Dec-2014	N/A	Correspondence - Email		M. Usher requests that Midcycle communication include CSS updates
2-Dec-2014	N/A	Correspondence - Email		Email of Sequence 0011
2-Dec-2014	0011	Submission - Response to FDA Request #10		Response to FDA Request #10; Exposure information
3-Dec-2014	N/A	Correspondence - Email		M. Usher emails supplementary information for Seq 0011 that was provided by J&JPRD for Study EDI1001
3-Dec-2014	0012	Submission - Response to FDA Request #11		Response to FDA Request #11; Metabolism information
4-Dec-2014	N/A	Correspondence - Email	FDA Request #12	FDA Requests rationale for including risk factors of pancreatitis and SO spasm in contraindication; asks for withdrawal AE information in the single blind withdrawal phase of Study 3002
8-Dec-2014	N/A	Correspondence - Email		M. Usher notifies FDA by email of intention to withdraw the proprietary name of XENRYMA and asks if acceptable to submit two names (one primary and one alternative)
8-Dec-2014	N/A	Correspondence - Email		M. Usher requests status of the agenda and call information for the Midcycle Communication Meeting

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
9-Dec-2014	N/A	Correspondence - Email	FDA Request #13	FDA provides Midcycle Communication meeting agenda confirming no major safety issues, no REMs and no Ad Comm plans. Denotes two review issues: imbalance of pain adverse events and feasibility to market the 75 mg dose for those pts intolerant of the 100 mg dose; Requests additional Clinical Pharmacology and Chemistry Information.
9-Dec-2014	N/A	Correspondence - Email		Provides email of response to FDA Request #12; Risk factors in contraindications; Withdrawal AE information
9-Dec-2014	0013	Submission - Response to FDA Request #12		Response to FDA Request #12; Risk factors in contraindications; Withdrawal AE Information,
10-Dec-2014	N/A	Correspondence - Email		FDA provides names of attendees attending the Midcycle Communication meeting
12-Dec-2014	0014	Submission - Response to FDA Request #9		Response to FDA Request #9. Label revisions.
22-Dec-2014	N/A	Correspondence - Email		FDA will allow the submission of two names for proprietary review but will only review the primary name
23-Dec-2014	0015	Submission - Withdrawal of Proprietary Name of XENRYMA; Request for Proprietary Name Review		Withdraw name of XENRYMA; Request review of IBSENDA (primary) and VIBERZI (alternate) as proprietary name
24-Dec-2014	N/A	Correspondence - Email	FDA Request #14	Additional Clinical Pharmacology Requests: 1. Please provide justification for your choice of concentration in your protein binding study. 2. Please clarify if you have evaluated the induction potential of CYP2B6 by eluxadoline (JNJ-27018966). 3. Please clarify if you have evaluated the inhibition potential of CYP2C8 by eluxadoline (JNJ-27018966).
24-Dec-2014	N/A	Correspondence - Email		Furiex requests an extension in providing response to FDA Request #14
30-Dec-2014	N/A	Correspondence - Email		FDA Accepts extension for response to Request #14

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
31-Dec-2014	N/A	Correspondence - Letter		FDA acknowledgement of Proprietary Name Request Withdrawal and submission of new name of IBSENDA. Denotes new user fee goal date for review of name of 23 March 2015.
5-Jan-2015	N/A	Correspondence - Email		Email response (Seq 0016) to FDA Request #14
8-Jan-2015	0016	Submission - Response to Clinical Pharmacology Request for Information (See FDA Request #14)		Response to FDA Request #14
9-Jan-2015	N/A	Correspondence - Telephone Contact		Discussion between Ms. Usher (Furiex) and Ms. Sarchet (FDA) regarding follow up to the Midcycle Meeting including feasibility of marketing the 75 mg dose in addition to the 100 mg and potential to speak with CSS reviewer.
9-Jan-2015	0017	Submission - Response to CMC RFI (See FDA Request #13)		Response to FDA Request #13 - CMC information
12-Jan-2015	0018	Submission - Follow up to Midcycle Communication Meeting (see FDA Request #13)		Provides sponsor version of Midcycle Communication Meeting Minutes; Follow-up responses from Meeting and Response to Clin Pharm Request for Information (see FDA Request #13)
13-Jan-2015	N/A	Correspondence - Email	FDA Request #15	FDA's version of Midcycle Communication Meeting minutes. Also CSS provides post note comments which include dependence assessment information request
16-Jan-2015	N/A	Correspondence - Email	FDA Request #16	FDA Clinical information requests: expand AE terms (see submission Seq 0018); analysis of AEs for those pts who took loperamide; IVR clarification
16-Jan-2015	N/A	Correspondence - Email	FDA Request #17	FDA Statistical Information request for a per protocol analysis for 3001/3002 removing pts with protocol violations for primary and secondary endpts
20-Jan-2015	N/A	Correspondence - Email		Furiex confirms receipt of FDA Information Requests #16 and #17 and asks status of response to questions submitted in Seq 0018 (submitted on 12 Jan 2015)

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
21-Jan-2015	N/A	Correspondence - Email		FDA responds to questions in Seq 0018: confirms that adding the 75 mg dose to the label is not considered a major amendment impacting the NDA review clock. Also indicates that CSS is meeting on 22 Jan to review questions in Seq 0018 about a potential meeting. FDA asks what would be the format of the CSS meeting
21-Jan-2015	N/A	Correspondence - Email		Furiex requests further response to proposal for administering the 75 dose as stated in Seq 0018 and requests strategy for the submission of the label. Furiex also requests that the meeting be a f2f meeting but would accept a teleconference.
21-Jan-2015	N/A	Correspondence - Email	FDA Request #18	FDA requests the word version of the final approved PSP, the deferral and waiver requests
22-Jan-2015	N/A	Correspondence - Email (Response to FDA Request #18)		Response to FDA Request #18: Furiex provides the PSP, deferral and waiver requests in Word format
26-Jan-2015	N/A	Correspondence - Email		FDA confirms by email acceptance of the proposal for adding the 75 mg to the label
26-Jan-2015	N/A	Correspondence - Email	FDA Request #19	FDA requests if a CYP3A4 substrate study has been conducted and requests clarification if 27018966 – 23086098 are the same cmpd. FDA also requested dose-proportionality in patient population using the PK data from phase 2 dose ranging study.
27-Jan-2015	N/A	Correspondence - Email		Furiex requests timing of revised labeling from FDA to add the 75 mg data.
27-Jan-2015	N/A	Correspondence - Email		Furiex responds to FDA Request #15; CSS withdrawal AE info broken down by study
28-Jan-2015	N/A	Correspondence - Email		Furiex provides email response to FDA Request #19 (Seq 0019).
28-Jan-2015	N/A	Correspondence - Email	FDA Request #20	FDA supplies revised labeling for Furiex to add the 75mg data to and requests revised label by 18 Feb 2015.
28-Jan-2015	N/A	Correspondence - Email		Furiex denotes to FDA that their revised labeling comments contradicts comments previously provided by FDA earlier
29-Jan-2015	N/A	Correspondence - Email		Furiex requests status of CSS meeting date.

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
30-Jan-2015	0019	Submission - Response to Information Request (Clinical, Statistics, Clinical Pharmacology)		Response to FDA Request 16, 17 and 19. Also clarified missing pt info in ISS listing 2.5.
2-Feb-2015		Correspondence - Email		Furiex requests status of CSS meeting date.
2-Feb-2015		Correspondence - Email		Furiex requests status of late cycle meeting logistics
2-Feb-2015		Correspondence - Email	FDA Request #21	FDA Request for Information (CMC) for tightening dissolution specifications
2-Feb-2015		Correspondence - Email		Furiex requests an extension in providing the response on 06 Feb 2015
3-Feb-2015		Correspondence - Email		FDA accepts extension of 06 Feb for supplying CMC response to FDA Request #21
3-Feb-2015		Correspondence - Letter		FDA denies the proprietary name of IBSENDA and requests that we resubmit the alternate name for consideration
5-Feb-2015		Correspondence - Email		Furiex emails response to FDA Request #21 (Seq 0020)
9-Feb-2015		Correspondence - Email		Furiex requests status of CSS meeting date.
10-Feb-2015		Correspondence - Letter		FDA supplies a date of 25 Feb 2015 (from 3-4pm) as a proposed date for the CSS meeting. Furiex requests status of CSS questions.
11-Feb-2015		Correspondence - Email	FDA Request #22	FDA requests a teleconference on 12 Feb 2015 to discuss additional CMC questions concerning diisopropylethylamine and certain methods/validation reports for both API and DP
11-Feb-2015	0020	Submission - Response to Information Request (CMC)		Response to FDA Request #21 concerning tightening dissolution specifications for the drug product.
12-Feb-2015	0021	Submission - Request for Proprietary Name		Request for the review of VIBERZI as the proprietary name
12-Feb-2015		Correspondence - Email		Furiex supplies preliminary responses (response to FDA Request #22) in advance of the 12 Feb 2015 CMC FDA teleconference
12-Feb-2015		Correspondence - Email		Furiex again requests status of alternative dates for CSS meeting and late cycle meeting logistics

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
12-Feb-2015		Contact Report - Meeting Minutes		Meeting minutes from 12 Feb 2015 FDA CMC Teleconference
12-Feb-2015		Correspondence - Email	FDA Request #23	FDA requesting assessment of the in vivo relevance of the interaction of the inhibition of CYP3A4 substrates; information in dataset for P2 PK
12-Feb-2015		Correspondence - Email	FDA Request #24	FDA/CSS requesting further CMC/nonclinical and clinical information by 20 Feb 2015
12-Feb-2015		Correspondence - Email		Furiex confirms 25 Feb 2015 CSS meeting date and asks for names of FDA attendees
13-Feb-2015		Correspondence - Email	FDA Request #25	FDA/CSS requesting data comparing eluxadoline to loperamide
13-Feb-2015		Correspondence - Email		FDA/CSS provides "Talking Points" for which they would like to discuss at CSS meeting on 25 Feb 2015
17-Feb-2015		Correspondence - Email		Furiex requests name/address of where to send packaging samples to and FDA replies to send them directly to Jennifer Sarchet (FDA)
17-Feb-2015		Correspondence - Email		FDA clarifies labeling requirements for sample blister packs
17-Feb-2015	022	Submission - Revised Labeling		Submission of revised labeling
17-Feb-2015		Correspondence - Email	FDA Request #26	FDA requests subgroup analyses (<66 years/>65 years) and baseline characteristics for 18 to 40 years, 41 to 64 years, and ≥ 65 years
17-Feb-2015		Correspondence - Email		Furiex responds to FDA Request #23 by email and commits to provide formal submission on 18 Feb.
18-Feb-2015	023	Submission - Response to Clinical Pharmacology Request for Information		Furiex provides response to FDA Request #23, Clinical Pharmacology
18-Feb-2015		Correspondence - Letter		J. Shay (Actavis) sends the packaging samples to J. Sarchet (FDA) (see FDA Request #15)
19-Feb-2015		Correspondence - Email		Furiex provides email response to FDA Request #22 (follow- up to CMC teleconference held on 12 Feb 2015)
20-Feb-2015	024	Submission - Response to CMC Request for Information		Formal response to FDA Request #22 (follow-up to CMC teleconference held on 12 Feb 2015)

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
20-Feb-2015		Correspondence - Email		Furiex provides email response to FDA Request #24 and #25 concerning abuse assessment data
23-Feb-2015		Correspondence - Email		M.Usher forwards three additional attachments that were inadvertently left out of the 20 Feb 2015 email response to CSS RFI
24-Feb-2015		Correspondence - Letter		FDA grants Type C meeting with CSS
24-Feb-2015	025	Submission - Response to CSS Request for Information		Furiex provides response to FDA Request #24 and #25 and outlines points for discussion for meeting to be held on 25 Feb 2015 with FDA/CSS
25-Feb-2015		Correspondence - Email		Furiex provides email response to FDA Request #26 regarding age subgroup analysis (Seq 0026)
25-Feb-2015		Contact Report: Meeting Minutes with CSS (25 February 2015)	FDA Request #27	Type C Meeting held on 25 Feb 2015 with CSS. FDA requests that we revise the Abuse Evaluation Report including the 8-factor to denote Schedule IV and include the animal IV tox information.
27-Feb-2015	026	Submission - Response to Clinical/Statistical Request for Information		Furiex provides response to FDA Request #26 concerning age subgroup analyses and baseline characteristics
27-Feb-2015		Correspondence - Email		Follow-up to Type C meeting held on 25Feb2015: Furiex provides location of certain information in IV tox reports requested during meeting
4-Mar-2015		Contact Report - Late Cycle Meeting Plans		FDA denotes ahead of Late Cycle Meeting that there are no plans for an Advisory Committee meeting and no REMS will be required for NDA approval.
4-Mar-2015		Correspondence - Letter		FDA provides the Late Cycle Meeting Background Package and proposed meeting attendees from FDA
6-Mar-2015		Correspondence - Letter		FDA's version of Meeting Minutes from 25 Feb 2015 meeting held with CSS
11-Mar-2015	027	Submission - Response to CSS Request for Information		Response to FDA Request #27: Follow up to Type C meeting - Submission of revised Abuse Evaluation Report denoting Schedule IV recommendation and proposed Section 9 labeling

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
11-Mar-2015		Contact Report - Late Cycle Meeting Minutes	FDA Request #28	Sponsor's version of meeting minutes from Late Cycle Meeting held on 11 March 2015. FDA requests safety review of patients taking certain conmeds.
17-Mar-2015	028	Submission - Response to Clin Pharm Request for Information		Response to FDA Request #28: Review of AE profile of patients taking certain conmeds to determine clinical relevance for proposed labeling. Furiex also provides meeting minutes from LCM meeting and suggested revised W&P labeling wording that succinctly summarizes the SO spasms/pancreatitis/hepatic enzyme elevations.
17-Mar-2015		Correspondence - Email		FDA requests clarification of footer in Pgp substrate tables from submission Seq 0028
18-Mar-2015		Correspondence - Email		Furiex confirms typographical error in footer of Pgp substrate tables and denotes that data are not impacted by this error. Furiex corrects typo and resends by email the corrected footer.
30-Mar-2015		Correspondence - Email		FDA follows up to Late Cycle Meeting clarification regarding the proposed dissolution testing PMC.
3-Apr-2015		Correspondence - Email		FDA indicates that they are targeting to provide the label by 30 April 2015. Furiex requests to clarify if FDA will still be providing preliminary comments on the clinical section of the labeling in advance of 30 April 2015 as was discussed during the Late Cycle Meeting
10-Apr-2015		Correspondence - Letter		FDA version of Late Cycle Meeting Minutes
14-Apr-2015		Correspondence - Email		Ms. Davis-Williams clarifies that the final label including clinical comments will be provided by 30 April 2015
28-Apr-2015		Correspondence - Letter		FDA accepts proprietary name of VIBERZI
29-Apr-2015		Correspondence - Email	FDA Request #29	FDA requests information from P3 trials for Snapshot
28-Apr-2015		Correspondence - Email		Furiex requests a teleconference to discuss pending labeling comments
30-Apr-2015		Correspondence - Email	FDA Request #30	FDA provides final label in track changes and asks for response by 07 May 2015

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30-Apr-2015		Correspondence - Email	FDA Request #31	FDA provides proposed PMRs/PMCs and asks for a response by 04 May 2015
30-Apr-2015		Correspondence - Email		FDA indicates that dissolution PMC may be coming later.
1-May-2015		Correspondence - Email		Email correspondence initiating on 30 April asking FDA for a teleconference to discuss labeling comments and proposed questions were sent on 01 May 2015
1-May-2015		Correspondence - Email		Furiex requests status of CSS assessment and their preliminary scheduling decision. FDA responds that the review is complete and has concluded that eluxadoline has abuse potential; the scheduling process has been initiated and that no further information will be provided until DEA publishes the notice about scheduling
1-May-2015		Correspondence - Email		FDA confirms that iPSP dates can be modified upon PMR/PMC negotiations
1-May-2015		Correspondence - Email		CSS provides explanation for not using sponsor proposed text for Section 9 of the label
1-May-2015		Correspondence - Email		FDA confirms that response to the SnapShot RFI needs to be formally submitted to the NDA as well as emailed.
4-May-2015		Correspondence - Email		Furiex emails Seq 0029 (response to FDA Request #31: PMCs/PMRs)
4-May-2015		Correspondence - Email		FDA denotes that labeling clarification will be made in writing rather than a teleconference.
4-May-2015	0029	Response to Request for Information/PMC & PMRs		Formal response to FDA Request #31 providing dates proposed for the PMCs/PMRs
4-May-2015		Correspondence - Email		Furiex attempts to get a dereference to discuss labeling comments prior to the 07 May response date
5-May-2015		Correspondence - Email		FDA provides written response to reasonings for the deletion of certain text in the clinical trials section of the label
7-May-2015		Correspondence - Email		Response to FDA Request #32:Furiex emails proposed labeling
7-May-2015	0030	Response to Request for Information/Proposed Labeling		Response to FDA Request #32 that supplies revised PI and MG with supporting rationale for not accepting certain FDA changes in Section 14 of the label

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8-May-2015		Correspondence - Email		Furiex notifies FDA of error in Cover letter to Seq 0030 and provides a copy of the corrected cover letter as Seq 0031 by email
8-May-2015	0031	Correction to Cover letter for Sequence 0030		Correction of the cover letter of Sequence 0030 that supplies the cumulative distribution figures and rationale for urgency/frequency that were inadvertently left out of the earlier cover letter
8-May-2015		Correspondence - Email	FDA Request #32	FDA supplies the Biopharm PMC for dissolution assessments and requests comments
13-May-2015		Correspondence - Email	FDA Request #33	FDA supplies additional labeling comments and requests feedback by 14 May 2015
13-May-2015		Correspondence - Email		Furiex requests teleconference to discuss labeling comments provided on 30 April and 13 May before sponsor is able to respond by 14 May
13-May-2015		Correspondence - Email		Furiex provides by email the response to FDA Request #32 (Biopharm PMC)
13-May-2015	0032	Response to Request for Information/Clinical Trial Data for Snapshot Website		Furiex provides response to FDA Request #29; clinical trial data for FDA website SNAPSHOT
14-May-2015		Correspondence - Email		Furiex requests status of requests for teleconference to discuss labeling comments
14-May-2015		Correspondence - Email		Furiex provides examples of FDA labeling comments provided recently that contradict earlier feedback
14-May-2015	0033	Response to Request for Information/Biopharm PMC		Furiex provides response to FDA Request #32 (Biopharm PMC)
15-May-2015		Correspondence - Email		FDA asks that sponsor hold off submitting response to labeling comments (FDA Request #33) until receipt of further follow up from FDA.
15-May-2015		Correspondence - Email		Furiex attempts clarification to email from FDA dated 01 May 2015 regarding not disclosing pending scheduling recommendation to sponsor until after DEA publication in Federal Register

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
18-May-2015		Correspondence - Email		Email of Response to FDA Request #33; Proposed Labeling
18-May-2015	0034	Response to Request for Information/Proposed Labeling		Response to FDA Request #33: Proposed Labeing
19-May-2015		Correspondence - Email	FDA Request #34	Furiex asks if FDA has any comments on proposed labeling for the bottle/blister/carton. FDA requests that we submit the revised labeling indicating the new name.
19-May-2015		Correspondence - Email	FDA Request #35	FDA asks that we confirm the Biopharm PMC
20-May-2015		Correspondence - Email		FDA grants teleconference to discuss labeling for 21 May from 9:30 - 10:00 eastern
20-May-2015		Correspondence - Email	FDA Request #36	FDA responds to Furiex email of 15 May 2015 requesting disclosure of pending scheduling decision and requests written confirmation that Furiex will not market VIBERZI until final scheduling from DEA
20-May-2015		Correspondence - Email		Response to FDA Request #36: Furiex provides written confirmation that they will not market VIBERZI until final scheduling from DEA per Form FDA 356h
20-May-2015		Correspondence - Email		Furiex provides proposed agenda for the 21 May teleconference
20-May-2015		Correspondence - Email		FDA provides summary document to faciliate discussions for the 21 May teleconferene which provides their preliminary feedback on labeling proposed in Seq 0034
21-May-2015		Meeting Minutes - Teleconference		Meeting minutes from 21 May 2014 teleconference with FDA to discuss labeling comments
21-May-2015		Correspondence - Email		Email Seq 0035 providing response to FDA Request #34
21-May-2015	0035	Response to Information Request - Proposed Contain/Carton Labeling		Response to FDA Request #34 which provides revised container/carton labeling
21-May-2015		Correspondence - Email	FDA Request #37	FDA provides edits to labeling based on teleconference

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
22-May-2015		Correspondence - Email	FDA Request #38	FDA provides feedback to proposed carton/container label (Seq 0035) and requests further changes
22-May-2015		Correspondence - Email	FDA Request #39	FDA provides final clinical/clinical pharmacology PMCs/PMRs for final confirmation/agreement. Furiex responds with agreement.
22-May-2015		Correspondence Email		Response to FDA Request #37 and #38; Email of Seq 0036
22-May-2015	0036	Response to Request for Information/Proposed Labeling; Revised Container/Carton Labeling		Response to FDA Request #37 and #38; Proposed labeling and revised carton/container labeling
22-May-2015		Correspondence - Email	FDA Request #40	FDA comments on "time to onset of effect" language proposed in Seq 0036
26-May-2015		Correspondence - Email		Response to FDA Request #35: Furiex agrees with final Biopharm PMC
26-May-2015		Correspondence - Email		Response to FDA Request #40: Furiex provides a response regarding correlation to "time to onset of effect" data to durability data
26-May-2015		Correspondence - Email	FDA Request #41	FDA provides further revisions to labeling
26-May-2015		Correspondence - Email		Response to FDA Request #41: Email of Seq 0037
26-May-2015	0037	Response to Request for Information/Proposed Labeling		Response to FDA Request #41: Furiex accepts all edits proposed by FDA in their 26 May 2015 correspondence and provides requested information
26-May-2015		Correspondence - Email	FDA Request #42	FDA requests revisions to Snapshot data provided in Seq 0032 within 24 hrs. Furiex responds that this will require programming and will not be able to provide within timeframe requested. Furiex requests clarification as to how best to present safety demographic data considering misallocations, etc

Date	Serial # / Sequence	Document Type	FDA Request Number	Description of Contents
27-May-2015		Correspondence - Email		FDA sends an email indicating that further revisions will be forthcoming on the labeling. Furiex requests rationale for changes as FDA is revising text that they had sent the day before.
27-May-2015		Correspondence - Email	FDA Request #43	FDA provides final edits on PI and MG
		Correspondence - Email		Response to FDA Request #43; by email Furiex acknowledges the edits and informs FDA that the labeling is acceptable.
27-May-2015	0038	Response to Request for Information/Proposed Labeling		Response to FDA Request #43; Furiex formally submits to the NDA the final PI and MG
27-May-2015		Correspondence - Email	FDA Request #44	FDA provides the action letter acknowledging approval of VIBERZI with final PMRs/PMCs and requests SPL of the PI/MG within 14 days and the FPL of the container/carton
27-May-2015		Correspondence - Email		Furiex acknowledges receipt of approval letter
29-May-2015		Correspondence - Email		FDA provides further clarificaton to FDA Request #42
29-May-2015		Correspondence - Email		Furiex resquests to hold off with SPL and FPL until final scheduling decision
1-Jun-2015		Correspondence - Email		Response to FDA Request #42 by email (Seq 0039)
1-Jun-2015		Correspondence - Email		Furiex notifies FDA that the action letter failed to include the revised carton/container labels provided in Seq 0036 and asks if these labels are considered acceptable/final
2-Jun-2015	0039	Response to Request for Information/Data for FDA Snapshot Website		Response to FDA Request #42: Furiex provides data for SNAPSHOT website
2-Jun-2015		Correspondence - Email		FDA indicates that the revisions to the container/carton labels submitted in Seq 0036 were acceptable despite not being included with the 27 May action letter
2-Jun-2015		Correspondence - Email		FDA indicates that despite the pending scheduling decision, they want the SPL of the PI and MG within 14 days of approval. The SPL of the container/carton labels should be provided within 30 days of printing.

Exhibit 13

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16 July 2015

Donna Griebel, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products (DGIEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **VIBERZI™ (eluxadoline) Tablets (NDA 206940/Seq 0041)**
General Correspondence: Transfer of NDA Ownership

Dear Dr. Griebel:

Reference is made to NDA 206940 for VIBERZI (eluxadoline) Tablets submitted on 26 June 2014 by Furiex Pharmaceuticals, Inc (Furiex). The NDA was approved on 27 May 2015.

Please be advised that effective 16 July 2015, the ownership including all rights to the above referenced NDA has been transferred from Furiex Pharmaceuticals, Inc to Forest Tosara, Ltd. Forest Tosara, Ltd. has a complete copy of the approved application, including those records required per 21 CFR 314.72.

Forest Tosara, Ltd. will confirm its acceptance of the NDA transfer described above in a separate correspondence. Please direct all future communications regarding this NDA to:

Kathleen Waldron, MBA
Senior Director, Regulatory Affairs
Forest Laboratories, LLC
Harborside Financial Center, Plaza V
Jersey City, NJ 07311
(201) 386-2115 (tele)
(631) 858-7921 (fax)
kathleen.waldron@actavis.com

Should you have any questions regarding this transfer, please do not hesitate to contact me by phone at 919.459.8774 (office) or 919.818.7565 (cellphone), or by email at michelle.usher@furiex.com.

This submission has been electronically prepared by Actavis. For technical questions regarding this submission, please contact Ronnie Rajkumar by phone at 201.427.8930 or by email at ronnie.rajkumar@actavis.com. The eCTD submission was generated using eCTDXpress, version 3.3.3. The submission has been scanned for viruses using McAfee VirusScan Enterprise version 8.8.0.975.

Sincerely,

Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
Furiex Pharmaceuticals, Inc., a subsidiary of Actavis, plc

Forest Tosara LIMITED
A Division of Forest Laboratories Europe
PHARMACEUTICAL MANUFACTURERS, Unit 146, Baldoyle Industrial Estate, Grange Road, Dublin 13 Tel: +353-(0)1-832 1199 Fax: +353-(0)1-832 1200 Email:tosara@forest-labs.ie

July 16, 2015

Donna Griebel, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products (DGIEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA: **VIBERZI™ (eluxadoline) Tablets (NDA 206940/Seq 0042)**
Re: **General Correspondence: TRANSFER OF OWNERSHIP (Acceptance)**

Dear Dr. Griebel:

Reference is made to NDA 206940 for VIBERZI (eluxadoline) which was submitted on June 26, 2014 and approved on May 27, 2015.

As per 21 CFR 314.72, Forest Tosara, Ltd has assumed the ownership as well as all rights and responsibilities for NDA 206940. Forest Tosara, Ltd. confirms that it has received from Furiex Pharmaceuticals, Inc., a complete copy of the NDA and correspondence relating to the NDA.

Reference is also made to the July 16, 2015 letter from Furiex Pharmaceuticals, Inc. (Seq 0041) to the Agency transferring ownership of the referenced application to Forest Tosara, Ltd. effective July 16, 2015.

With this correspondence, Forest Tosara, Ltd. designates Forest Laboratories, LLC as our authorized US Agent. The corporate address for our US Agent is as follows:

Forest Laboratories, LLC
Morris Corporate Center III
400 Interpace Parkway
Parsippany, New Jersey 07054

The primary contact for NDA 206940 is provided below. All future correspondence regarding this NDA should be directed to Kathleen Waldron at the following address:

Kathleen Waldron, MBA
Senior Director, Regulatory Affairs
Forest Laboratories, LLC
Harborside Financial Center, Plaza V
Jersey City, NJ 07311
(201) 386-2115 (tele)
(631) 858-7921 (fax)

kathleen.waldron@actavis.com

We look forward to receiving the Division's acknowledgement of this transfer of ownership.

If there are any questions related to this submission, please contact me at + 353 1 4357707.

Sincerely,

Michael Mc Donald
Controller - Dublin Operations
Clonshaugh Business and Technology Park
Clonshaugh
Dublin 17
Ireland

Electronic Submission Specifications

The structure of this submission is based on the eCTD format in accordance with *"Final Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications", June 2008,* and according to specifications provided in "ICH M2 EWG Electronic Common Technical Document Specification -- ICH eCTD Specification v3.2.2, 16-July-2008".

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

Anti-Virus Program	McAfee VirusScan Enterprise
Program Version	8.8.0.975
Scan Engine Version	5700.7163
Date Virus Scan Completed	7/16/2015

The IT point of contact for this submission is:

Name	Kristopher Hayes
Phone Number	(201) 427-8216
Email Address	kristopher.hayes@frx.com

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16 July 2015

Donna Griebel, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products (DGIEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Subject: **IND 79,214; Serial No. 0160**
General Correspondence: Transfer of IND Sponsorship
VIBERZI (eluxadoline) Tablets

Dear Dr. Griebel:

Please be advised that effective 16 July 2015, the sponsorship of the referenced IND has been transferred from Furiex Pharmaceuticals, Inc to Forest Tosara, Ltd. Forest Tosara, Ltd will fulfill the obligations set forth in 21 CFR 312 for this IND application. Also, please note that at this time there are no clinical studies ongoing.

Forest Tosara, Ltd. will confirm its acceptance of the IND transfer described above in a separate correspondence. Please direct all future communications regarding this IND to:

Kathleen Waldron, MBA
Senior Director, Regulatory Affairs
Forest Laboratories, LLC
Harborside Financial Center, Plaza V
Jersey City, NJ 07311
(201) 386-2115 (tele)
(631) 858-7921 (fax)
kathleen.waldron@actavis.com

This submission has been electronically prepared by Actavis. For technical questions regarding this submission, please contact Ronnie Rajkumar by phone at 201.427.8930 or by email at ronnie.rajkumar@actavis.com. The eCTD submission was generated using eCTDXpress, version 3.3.3. The submission has been scanned for viruses using McAfee VirusScan Enterprise version 8.8.0.975.

If you have any questions regarding this transfer of sponsorship, please do not hesitate to contact me by phone at (919) 459-8774, or by email at michelle.usher@furiex.com.

Sincerely,

Michelle P. Usher, RAC
Executive Director, Regulatory Affairs
Furiex Pharmaceuticals, Inc., a subsidiary of Actavis, plc

Forest Tosara LIMITED
A Division of Forest Laboratories Europe
PHARMACEUTICAL MANUFACTURERS, Unit 146, Baldoyle Industrial Estate, Grange Road, Dublin 13 Tel: +353-(0)1-832 1199 Fax: +353-(0)1-832 1200 Email:tosara@forest-labs.ie

July 16, 2015

Donna Griebel, MD, Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products (DGIEP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

IND: **79,214 - eluxadoline tablets**
Re: **General Correspondence: TRANSFER OF SPONSORSHIP (Acceptance)**
Seq: **0161**

Dear Dr. Griebel:

Reference is made to the Investigational New Drug Application (IND) identified above for eluxadoline tablets.

Pursuant to 21 CFR 312.20-312.33, Forest Tosara, Ltd has assumed the sponsorship and all rights and responsibilities for the referenced IND. Forest Tosara, Ltd. confirms that it has received from Furiex Pharmaceuticals, Inc., a complete copy of the IND and correspondence relating to the IND.

Reference is also made to the July 16, 2015 letter from Furiex Pharmaceuticals, Inc. (Seq 0160) to the Agency transferring sponsorship of the referenced IND to Forest Tosara, Ltd. effective July 16, 2015.

With this correspondence, Forest Tosara, Ltd. designates Forest Laboratories, LLC as our authorized representative.

The primary contact for IND 79,214 is provided below. All future correspondence regarding this IND should be directed to Kathleen Waldron at the following address:

Kathleen Waldron, MBA
Senior Director, Regulatory Affairs
Forest Laboratories, LLC
Harborside Financial Center, Plaza V
Jersey City, NJ 07311
(201) 386-2115 (tele)
(631) 858-7921 (fax)
kathleen.waldron@actavis.com

We look forward to receiving the Division's acknowledgement of this transfer of sponsorship.

If there are any questions related to this submission, please contact me at + 353 1 4357707.

Sincerely,

Michael Mc Donald
Controller - Dublin Operations
Clonshaugh Business and Technology Park
Clonshaugh
Dublin 17
Ireland

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All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

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Program Version	8.8.0.975
Scan Engine Version	5700.7163
Date Virus Scan Completed	7/16/2015

The IT point of contact for this submission is:

Name	Kristopher Hayes
Phone Number	(201) 427-8216
Email Address	kristopher.hayes@frx.com