(12) STANDARD PATENT (11) Application No. AU 2012202459 B2
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Novel compounds as opioid receptor modulators

(51) International Patent Classification(s)
C07D 233/54 (2006.01) ***A61K 31/4178*** (2006.01)
A61K 31/4172 (2006.01) ***A61K 31/454*** (2006.01)

(21) Application No: **2012202459** (22) Date of Filing: **2012.04.27**

(43) Publication Date: **2012.05.17**
(43) Publication Journal Date: **2012.05.17**
(44) Accepted Journal Date: **2014.06.12**

(62) Divisional of:
2005224091

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(56) Related Art
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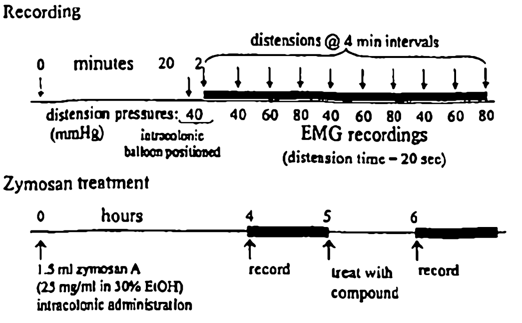
Abstract

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 disorders that may be ameliorated or treated by the modulation of opioid receptors.

Figure 1

Figure 1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distensions @ 4 min intervals
0 minutes 20 22
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(mmHg)
intracolonic balloon positioned
40 60 80 40 60 80 40 60 80
EMG recordings
(distension time - 20 sec)
Zymosan treatment
0 hours
4
5
6
1.5 ml zymosan A
(25 mg/ml in 30% EtOH)
intracolonic administration
record
treat with compound
record

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AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

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Invention Title: Novel compounds as opioid receptor modulators

Details of Original Application No. 2005224091 dated 14 Mar 2005

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

File: 51588AUP01

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NOVEL COMPOUNDS AS OPIOID RECEPTOR MODULATORS

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

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

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 overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

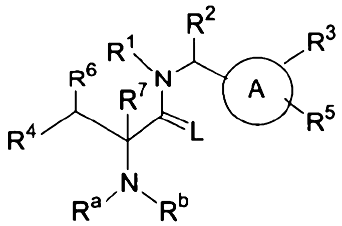
The present invention relates to opioid receptor modulators. The invention further relates to opioid receptor agonists and opioid receptor antagonists. The invention further relates to opioid receptor ligands that are selective for each type of opioid receptor, mu, delta and kappa. The invention further relates to opioid receptor ligands that modulate two or three opioid receptor types, mu, delta and kappa, simultaneously. The invention further relates to compounds that may be useful as intermediates in preparing new opioid receptor modulators. The invention further relates to a method of treating or ameliorating a condition mediated by an opoid receptor. The invention further relates to pharmaceutical composition comprising a compound of the present invention useful as an opioid receptor modulator.

Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

Although the invention will be described with reference to specific examples it will be appreciated by those skilled in the art that the invention may be embodied in many other forms.

Summary of the Invention

According to a first aspect of the present invention there is provided a 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;

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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 groupconsisting 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;

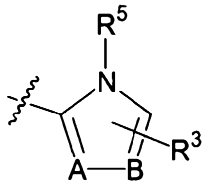
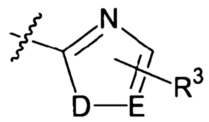
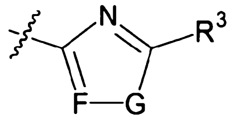
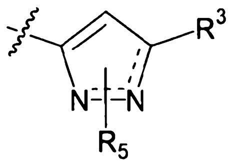
provided that no more than one R^{11} substituent is selected from the group consisting of C_{6-10}aryl(C_{1-6})alkyl; C_{6-10}aryl(C_{1-6})alkoxy; C_{6-10}aryl; heteroaryl optionally substituted with one to two substituents independently selected from the group consisting of C_{1-4}alkyl, C_{1-4}alkoxy, 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 selected from the group consisting of ring system **a-1**, **a-2**, **a-3**, and

a-4, optionally substituted with R^3 and R^5;

 ,  ,  and 

a-1 a-2 a-3 a-4

wherein

A-B is selected from the group consisting of 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,

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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

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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;

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and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof, with the proviso that the compound of Formula (I) is other than:

(a) a compound wherein R^1=H or methyl; R^2=CH_2-phenyl or CH_2-naphthyl; A=ring system a-2 wherein D-E=O-N; R^3=methyl; R^4=naphthyl; R^5=absent; R^6=R^7=H; R^a=H or methyl; R^b=H, methyl or alkoxycarbonyl; and L=O;

(b) a compound wherein R^1=H; R^2=methyl; A=ring system a-1 wherein A-B=N-N; R^3=hydroxyl substituted phenyl; R^4=phenyl; R^5= R^6=R^7=H; R^a=H; R^b=alkoxycarbonyl; and L=O.

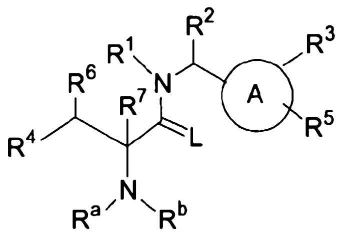
According to a second aspect of the present invention there is provided a composition comprising the compound as defined according to the first aspect of the present inveniton and a pharmaceutically acceptable carrier.

According to a third aspect of the present invention there is provided a method of making a composition comprising admixing the compound of the first aspect of the invention and a pharmaceutically acceptable carrier.

According to a fourth aspect of the present invention there is provided a method for treating or ameliorating a δ or μ-opioid receptor mediated disorder in a subject in need thereof comprising administerin to the subject a therapeutically effective amount of the compound of the first aspect of the present invention.

According to a fifth aspect of the present invention there is provided use of a compound as defined according to the first aspect of the inveniton, in the preparation of a medicament for treating or ameliorating a δ or μ-opioid receptor mediated disorder in a subject.

The present invention is directed to 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 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, hydroxyl(C_{1-6})alkyl, C_{1-6}alkoxy, hydroxyl, cyano, amino, C_1

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${}_{6}$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

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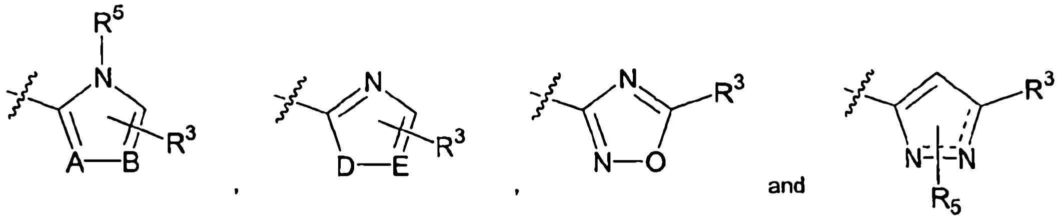
alkoxy substituents of aryl are optionally substituted with hydroxy, amino, C_{1-6}alkylamino, (C_{1-6}alkyl)$_2$amino, or aryl;

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 a-2 a-3 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

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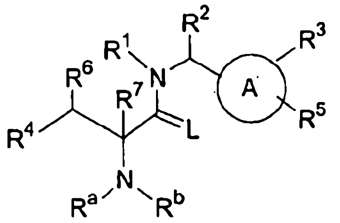
R^b are optionally taken together with the nitrogen to which they are both attached to form a five to eight membered monocyclic ring;

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;

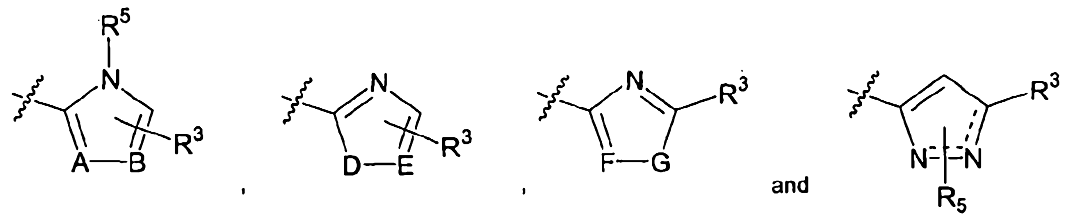
furthermore, wherein the aryl and heteroaryl portion of the R^1 substituents aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl, are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of C_{1-6}alkyl; hydroxy(C_{1-6})alkyl; C_{1-6}alkoxy; C_{6-10}aryl(C_{1-6})alkyl; 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, orC1-6 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 a-2 a-3 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;

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 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;

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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

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

Figure 2 and Figure 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.

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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.

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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 C1-6 alkoxycarbonyl, R^a and R^b are optionally taken together with the nitrogen atom

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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.

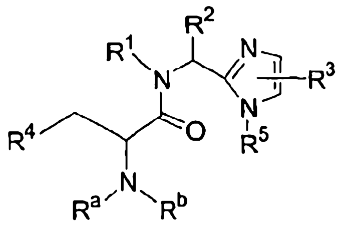
Embodiments of the present invention include those compounds wherein R^a and R^b are each hydrogen.

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, $C_{1\text{-}6}$alkyl, aryl($C_{1\text{-}4}$)alkyl, and heteroaryl($C_{1\text{-}4}$)alkyl;

wherein the aryl and heteroaryl portion of aryl($C_{1\text{-}4}$)alkyl and heteroaryl($C_{1\text{-}4}$)alkyl are optionally substituted with one to three R^{11} substituents independently selected from the group consisting of $C_{1\text{-}6}$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

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three substituents independently selected from the group consisting of chloro and carboxy;

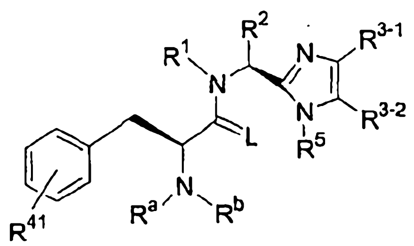
R^4 is phenyl substituted at the 4-position with hydroxy, C_{1-3}alkylaminocarbonyl, or aminocarbonyl, and optionally substituted with one to two substituents independently selected from the group consisting of methyl, methoxy, and benzyloxy;

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

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Cpd	R^1	R^2	$R^{3\text{-}1}$	$R^{3\text{-}2}$	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-(1*H*-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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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
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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

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Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

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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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

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Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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
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

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Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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-phenyl methyl	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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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) phenyl methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
121	Isopropyl	3-amino carbonyl phenyl methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
122	Isopropyl	3-cyano phenyl methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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
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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

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Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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
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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

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Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

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Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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-phenyl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
227	3-Carboxy-phenyl methyl	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-phenyl methyl	methyl	phenyl	H	H	H	H
232	3-Carboxy-4-methoxy-phenyl methyl	methyl	phenyl	H	H	2,6-dimethyl	H
233	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl	H

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Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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-phenyl methyl	methyl	4-chlorophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
238	3-Carboxy, 4-methoxy-phenyl methyl	methyl	4-fluorophenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
239	3-Carboxy-4-methoxy-phenyl methyl	methyl	4-chlorophenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
240	4-Carboxy-phenyl methyl	methyl	4-chlorophenyl	Me	H	2,6-dimethyl-4-aminocarbonyl	H
241	3-Carboxy-4-methoxy-phenyl methyl	methyl	4-chlorophenyl	Cl	H	2,6-dimethyl-4-aminocarbonyl	H
242	3-(1*H*-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-phenyl methyl	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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

Cpd	R[1]	R[2]	R[3-1]	R[3-2]	R[5]	R[41]	R[a] / R[b]
259	Benzyl	hydroxy methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
260	3-Carboxy-4-methoxy-phenyl methyl	methyl	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
261	3-Carboxy-4-methoxy-phenyl methyl	methyl	phenyl	H	H	4-hydroxy	H
262	3-Carboxy-4-methoxy-phenyl methyl	methyl	phenyl	H	H	4-hydroxy	H/ Me
263	3-Carboxy-4-methoxy-phenyl methyl	H	phenyl	H	H	4-hydroxy	H
264	3-Carboxy-4-methoxy-phenyl methyl	H	phenyl	H	H	4-hydroxy	H/ Me
265	3-Carboxy-4-methoxy-phenyl methyl	H	phenyl	H	H	2,6-dimethyl-4-hydroxy	H
266	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	H	H
267	3-(1*H*-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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

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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-(1*H*-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	Methoxy carbonyl

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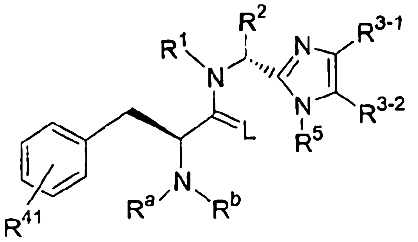
Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
311	2-Methoxycarbonyl-pyridin-4-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
312	4-Methoxycarbonylpyridin-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
313	6-Methoxycarbonyl-pyridin-2-ylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
315	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	Methoxy carbonyl
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

Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
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

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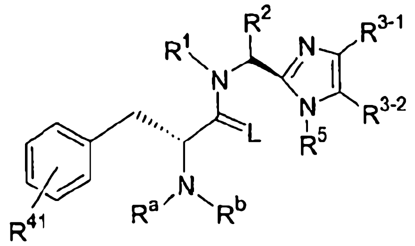
Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
280	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	H
281	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
282	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	2,6-dimethyl-4-aminocarbonyl	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):



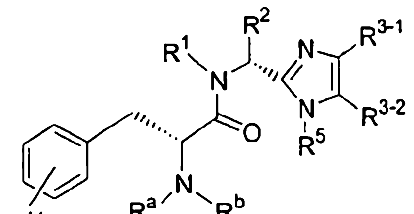
Formula (Id)

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-}

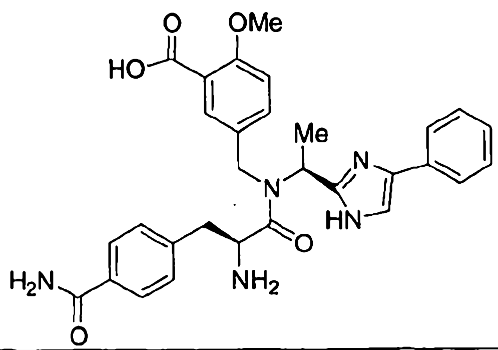
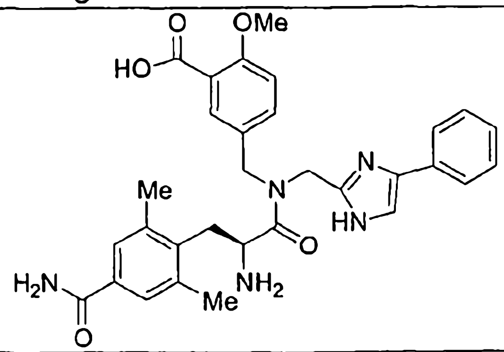
^{1}, R^{3-2}, R^5, R^a, R^b, and R^{41} are dependently selected from the group consisting of:

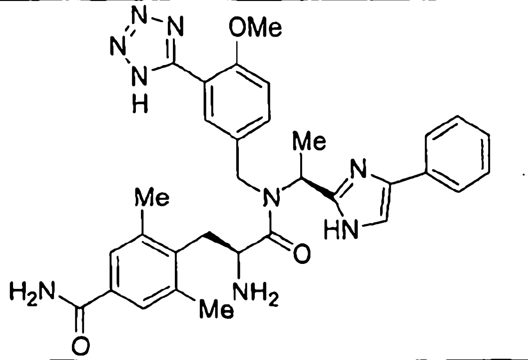
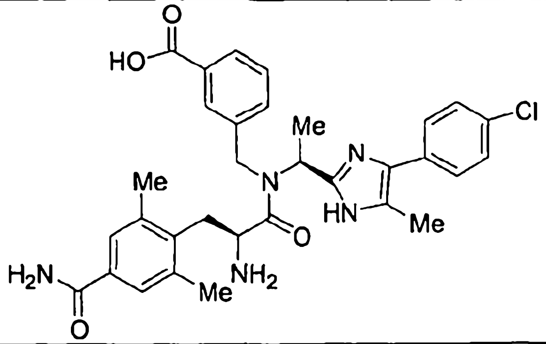
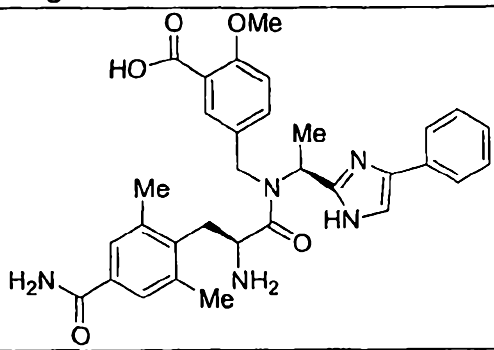
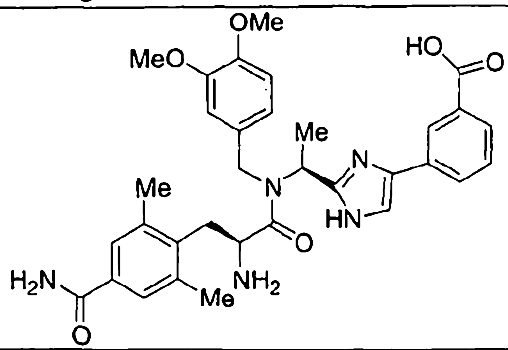
Table IV

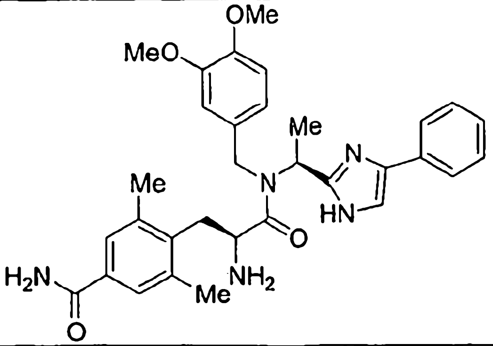
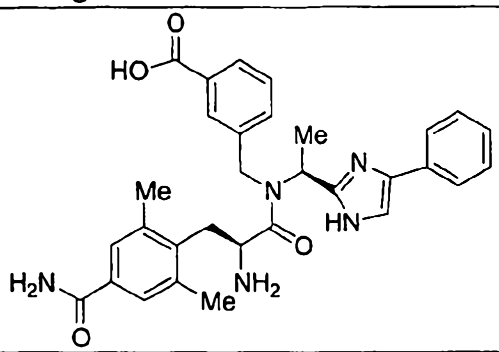
Cpd	R^1	R^2	R^{3-1}	R^{3-2}	R^5	R^{41}	R^a / R^b
284	3-Methoxycarbonyl-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H
285	3-Carboxy-4-methoxy-phenylmethyl	methyl	phenyl	H	H	4-aminocarbonyl	H

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

Table V

Cpd	
4	
6	

Cpd	
8	
12	
18	
20	

Cpd	
75	
227	

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** (Jan), *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.

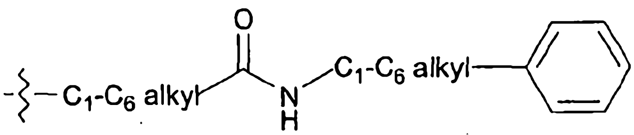
The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "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, moncyclic 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 2*H*-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

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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 moiety 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 areuseful 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), cross-linked 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.

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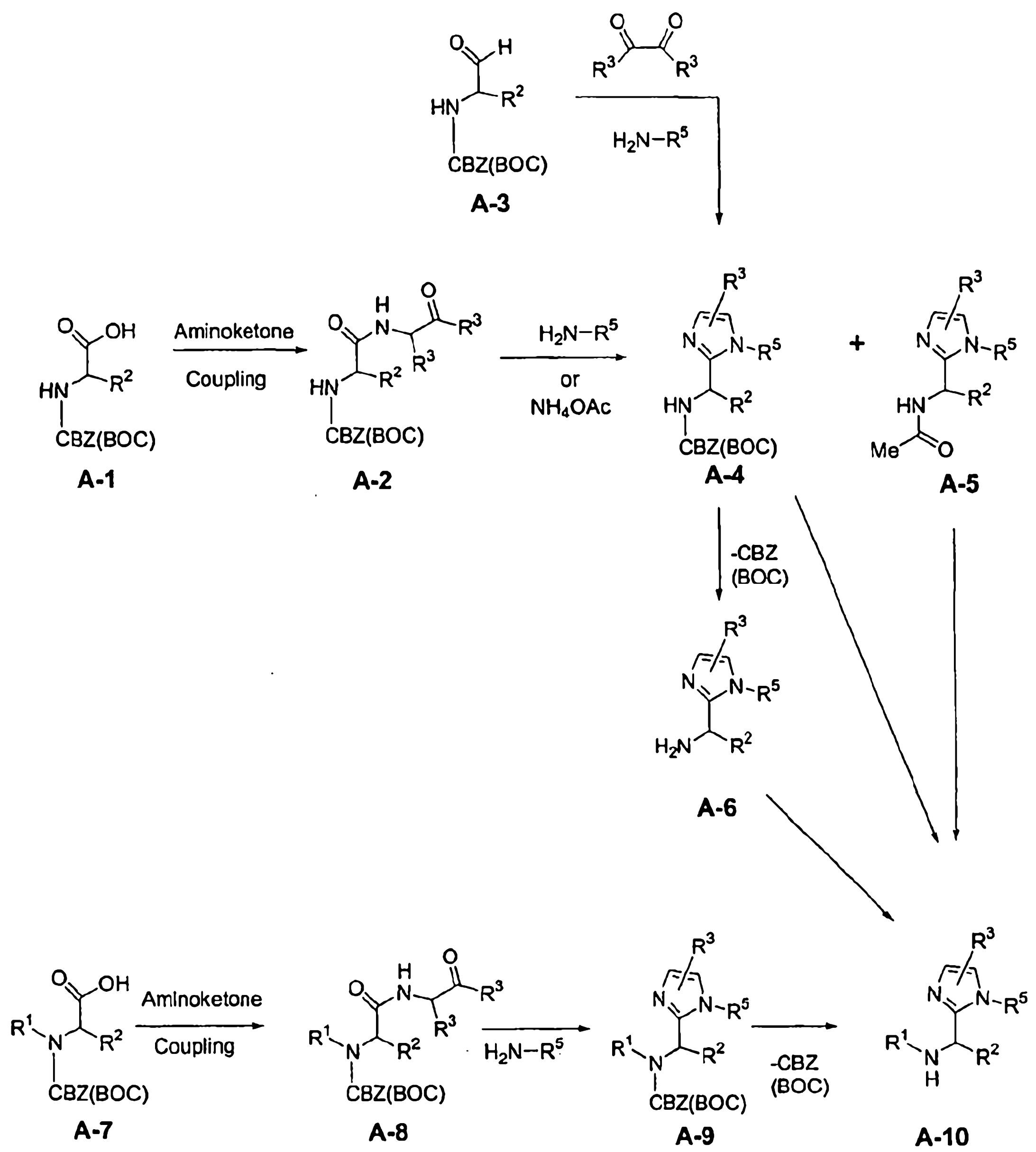
Scheme A



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.

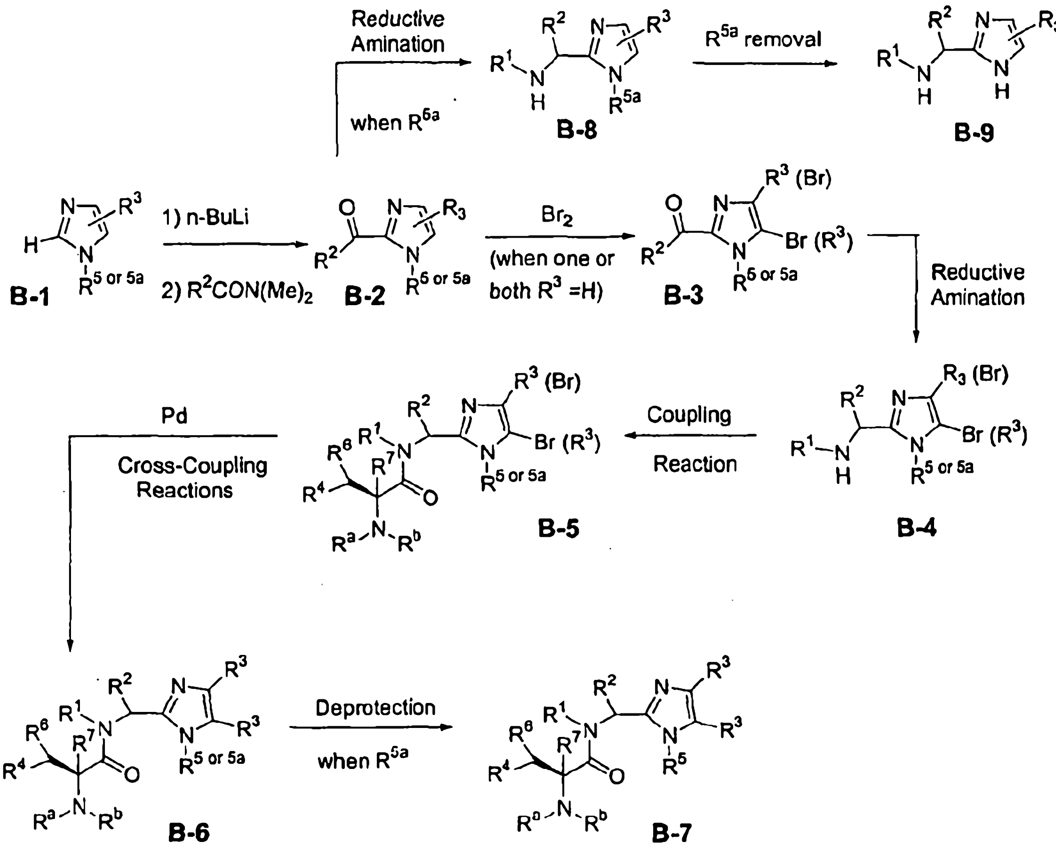
A compound of formula **A-6** may be substituted using reductive amination with an appropriately substituted aldehyde or ketone in the presence of a hydride source, such as sodium borohydride or sodium triacetoxyborohydride, provide compounds of formula **A-10**.

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 $H_2N\text{-}R^1$ 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**.

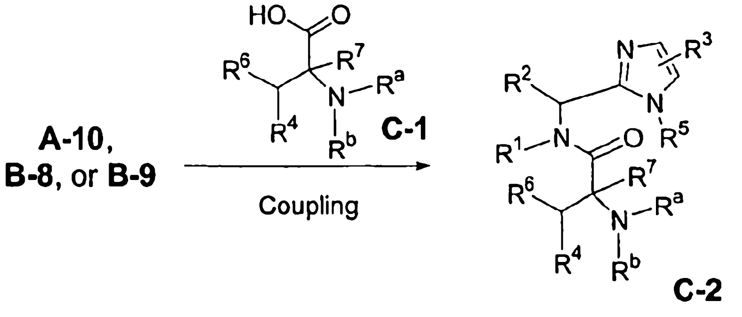
Certain R^3 substituents of the present invention in which a carbon atom is the point of attachment may be introduced into a compound of formula **B-5** through a transition metal-catalyzed cross coupling reaction to afford compounds of formula **B-6**. Suitable palladium catalysts include palladium 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 O 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.

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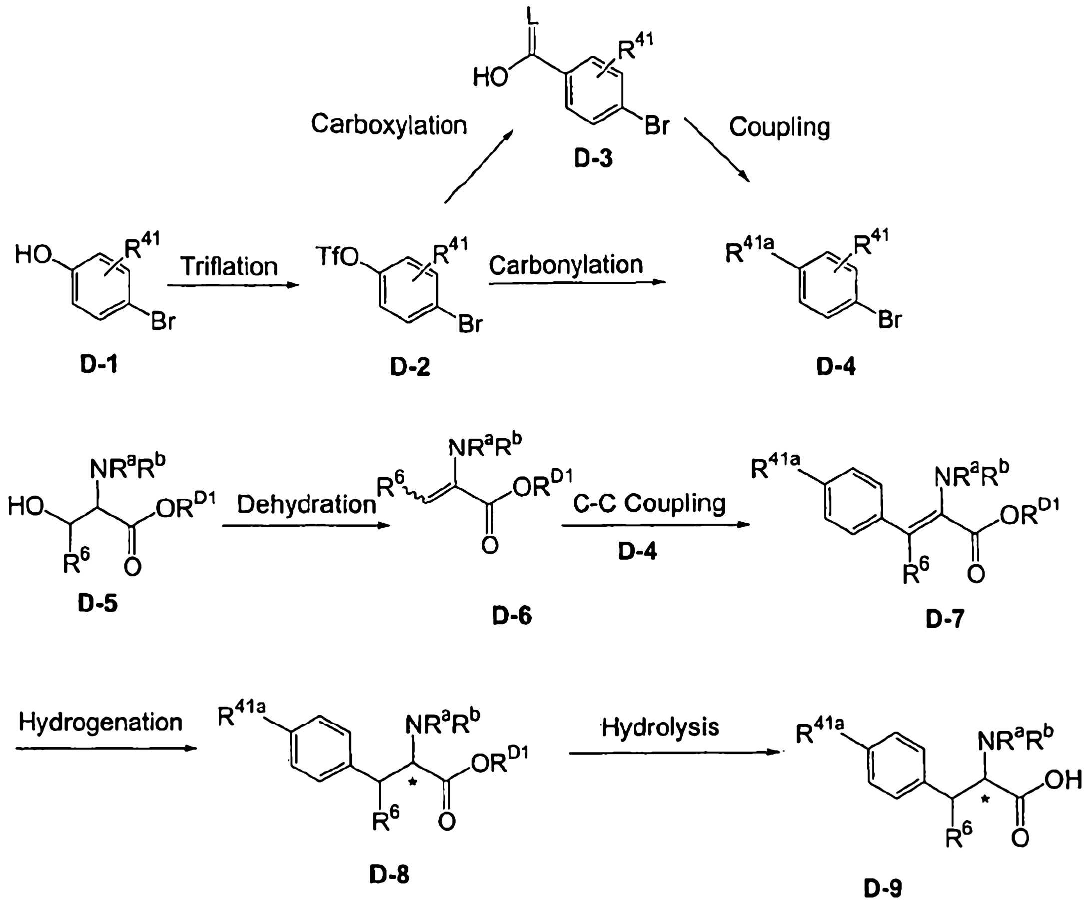
Scheme D



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

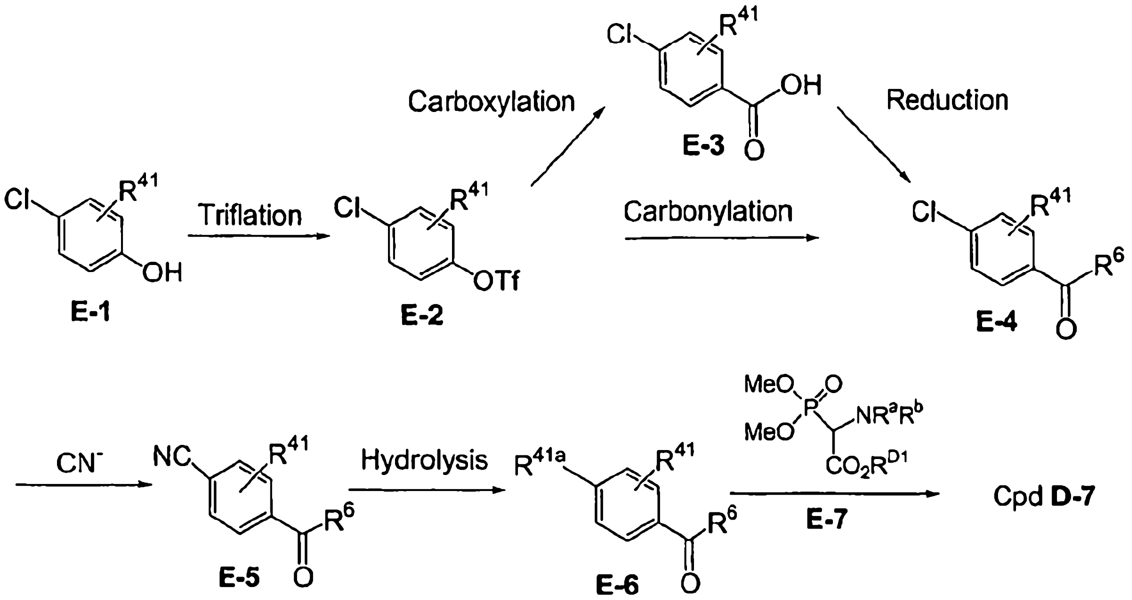
Specifically, a compound of formula **D-1** may be treated with trifluoromethanesulfonic anhydride to afford the triflate compound of formula **D-2**. A compound of formula **D-2** may be converted to a compound of formula **D-4** by a variety chemical routes which utilize conventional chemical methods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

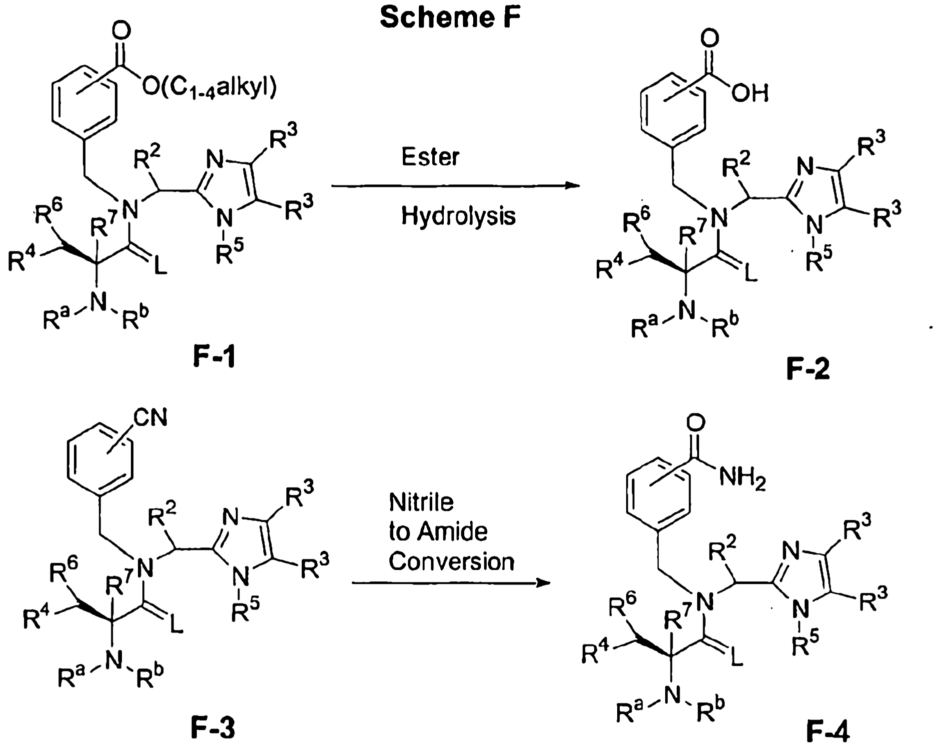
A compound of formula **E-4** may participate in a Horner-Wadsworth-Emmons reaction with a compound of formula **E-7** in the presence of an organometallic base such as *n*-butyllithiium to afford a compound of formula **D-7**. This intermediate may be further elaborated as described in Scheme D, herein.

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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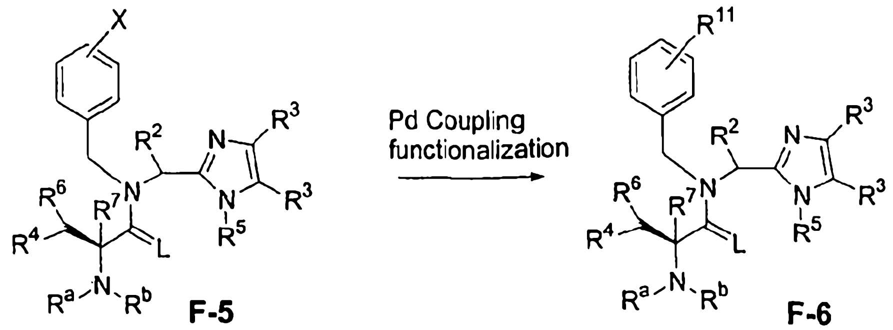

F-5 F-6

X= I, Br, -OTs, -OTf

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.

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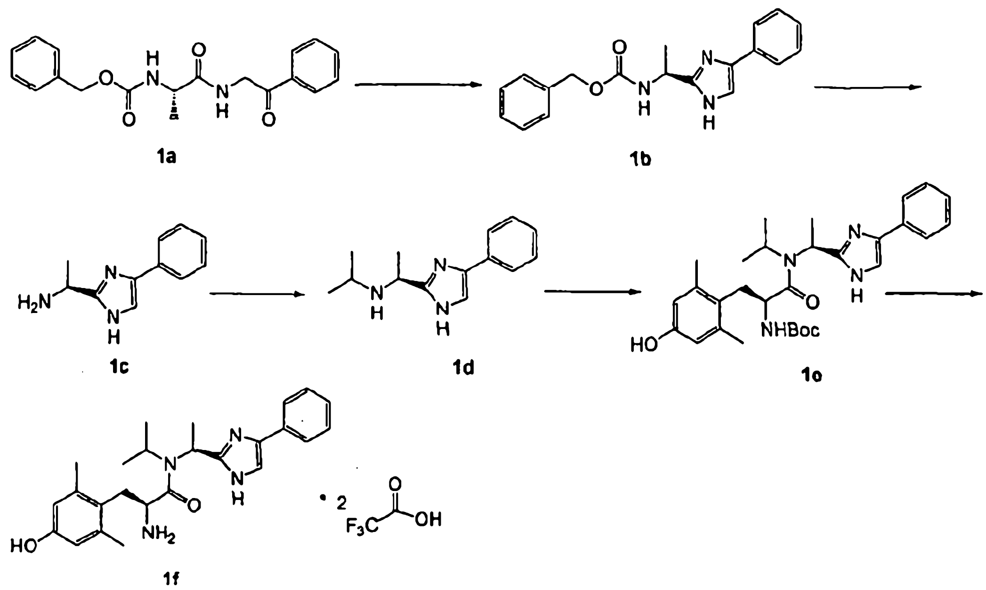
Specific Examples

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-1*H*-imidazol-2-yl)-ethyl]-propionamide



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 (1.62g, 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 %). ^{1}H 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-1*H*-imidazol-2-yl)-ethylamine.** To a solution of [1-(4-phenyl-1*H*-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-1*H*-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-1*H*-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-1*H*-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%).

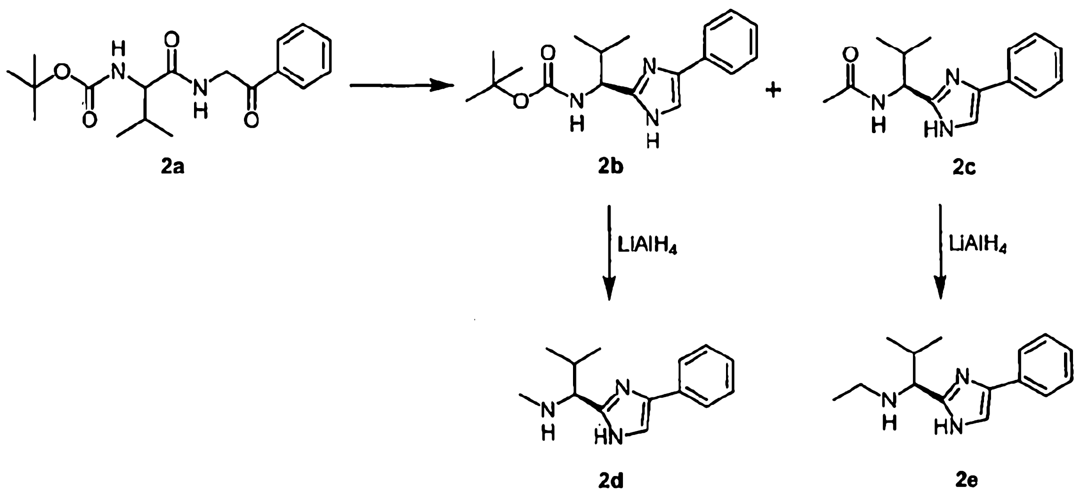
F. **2-Amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-N-isopropyl-N-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-propionamide.** A solution of (2-(4-hydroxy-2,6-dimethyl-phenyl)-1-{isopropyl-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-carbamoyl}-ethyl)-carbamic acid *tert*-butyl ester (0.13 g, 0.25 mmol) in trifluoroacetic 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-1 *H*-imidazol-2-yl)-propyl]-amine

and

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



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]-

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carbamic acid *tert*-butyl ester (Cpd **2b**), and 0.60 g of a mixture of N-[2-methyl-1-(4-phenyl-1 *H*-imidazol-2-yl)-propyl]-acetamide (Cpd **2c**) and acetamide.

Cpd **2c** was purified by dissolving it in hot CH_3CN and cooling to 0^oC. Collection of the precipitate by suction filtration afforded 0.21 g (7%) of N-[2-methyl-1-(4-phenyl-1*H*-imidazol-2-yl)-propyl]-acetamide, Cpd **2c**, as a white powder (HPLC: 100% @ 254 nm and 214 nm). ^1H 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).

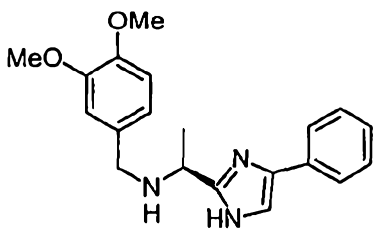
C. **Methyl-[2-methyl-1-(4-phenyl-1 *H*-imidazol-2-yl)-propyl]-amine.** A solution of [2-methyl-1-(4-phenyl-1-*H*-imidazol-2-yl)-propyl]-carbamic acid *tert*-butyl ester (0.095g, 0.30 mmol) in THF (2.0 mL) was added dropwise over 10 min to a refluxing 1.0 M solution of $LiAlH_4$ in THF (3.0 mL). The 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-1 *H*-imidazol-2-yl)-propyl]-amine as a light yellow oil (HPLC: 97% @ 254 nm and 214 nm). ^1H 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 (1 H, d, *J* = 6.3 Hz), 2.35 (3H, s), 2.06 (1 H, 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-1*H*-imidazol-2-yl)-propyl]-amine.** A solution of N-[2-methyl-1-(4-phenyl-1 *H*-imidazol-2-yl)-propyl]-acetamide (0.077g, 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 ^1H NMR) of ethyl-[2-methyl-1-(4-phenyl-1 *H*-imidazol-2-yl)-propyl]-amine and recovered Cpd **2c** as a colorless oil (HPLC: peaks overlap). ^1H 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-1 *H*-imidazol-2-yl)-propyl]-amine and ethyl-[2-methyl-1-(4-phenyl-1 *H*-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.

<u>Example 3</u>

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

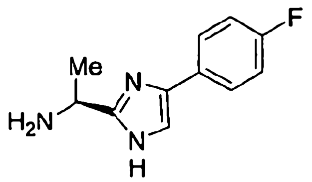


A solution of 1-(4-phenyl-1*H*-imidazol-2-yl)-ethylamine (0.061 g, 0.33 mmol) of Example 1, and 0.55 g (0.33 mmol) of 3,4-dimethoxybenzaldehyde in 5 mL of anhydrous methanol was stirred at room temperature for 1 h and then cooled to about 0-10°C in an ice bath for 1 h. The reaction was treated carefully 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-1 *H*-imidazol-2-yl)-ethyl]-amine as a light yellow oil (HPLC: 87% @ 254nm 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)-1*H*-imidazol-2-yl]-ethylamine



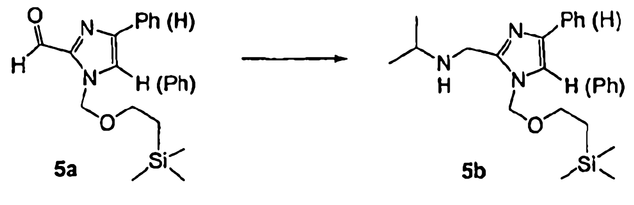
A. **{1-[4-(4-Fluoro-phenyl)-1*H*-imidazol-2-yl]-ethyl}-carbamic acid *tert*-butyl ester.** A mixture of ammonium acetate (19.3 g, 250 mmol) and glacial HOAc (35 mL) was stirred mechanically and heated to about 100°C to give a colorless solution in 5-10 min. After cooling to rt, a solid mixture of N-*t*-BOC-*L*-Alaninal (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 10u C18 250 x 50 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)-1*H*-imidazol-2-yl]-ethylamine.** {1-[4-(4-Fluoro-phenyl)-1*H*-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)-1*H*-imidazol-2-ylmethyl]-amine (mixture of regioisomers)



Mixture of regioisomers

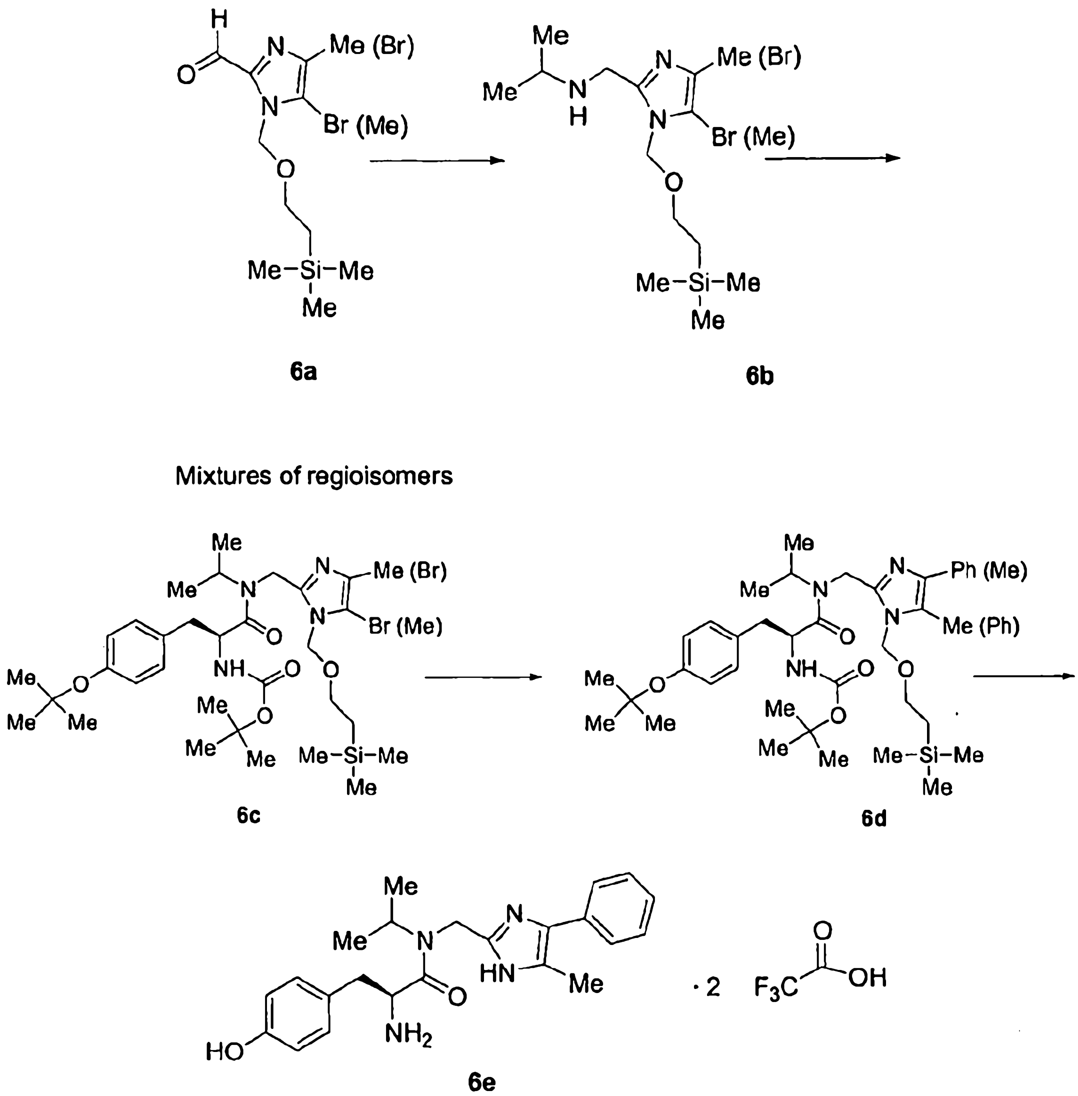
A. **Cpd 5a Regioisomers.** Into a cooled solution of 4(5)-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazole (*Tet. Lett.* **1986**, 27(35), 4095-8) (7.70 g, 28.1 mmol) in dry THF (60 mL) was added *n*-butyllithium (2.5 M in hexane, 22.5 mL, 56.2 mmol) at –78°C under N_2. The resulting mixture 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-1*H*-imidazol-2-ylmethyl)-propionamide Trifluoroacetate (1:2)



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)-1*H*-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

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(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. ^{1}H 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 (0.60g, 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

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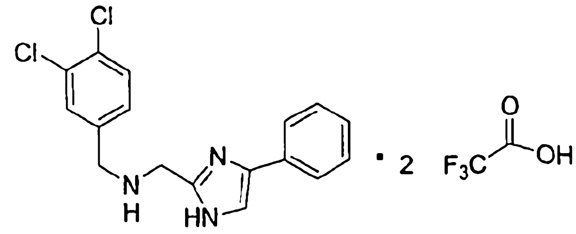
resulting mixture was degassed with N_2 for 5 min and then palladium tetrakis triphenylphosphine (53 mg, 0.046 mmol) was added neat. The reaction vessel was capped and warmed to 80°C for 14 h with rapid stirring. After cooling to room temperature the mixture was dried over $MgSO_4$, filtered through 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-1*H*-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 100 x 20 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-1*H*-imidazol-2-ylmethyl)-amine Trifluoroacetate (1:2)

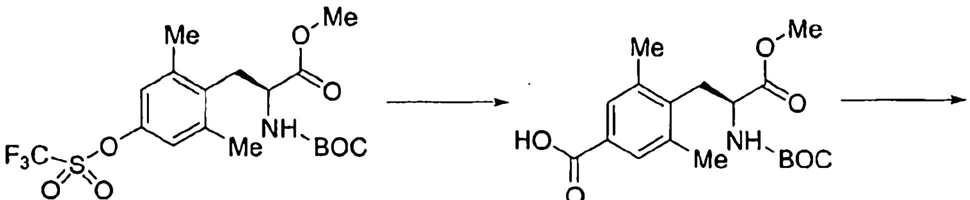


Using the procedure described in Example 5 and substituting 3,4-dichloro-benzylamine for isopropylamine, (3,4-dichloro-benzyl)-[4(5)-phenyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-imidazol-2-ylmethyl]-amine was prepared as a pair of regioisomers. A sample (95 mg, 0.21 mmol) of this compound was dissolved 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-1*H*-imidazol-2-ylmethyl)-amine as an off white lyophil.

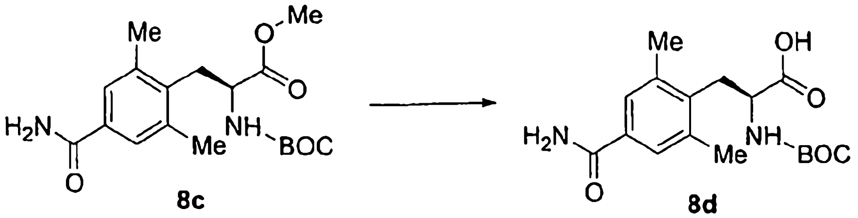
Following the procedure described in Example 1, substituting (3,4-dichloro-benzyl)-(4(5)-phenyl-1*H*-imidazol-2-ylmethyl)-amine for Cpd **1d**, compounds of the present invention may be synthesized with the appropriate reagents, starting materials, and purification methods known to those skilled in the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

Example 8

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



8a **8b**



8c 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 completion, 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; ^{1}H 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-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* =

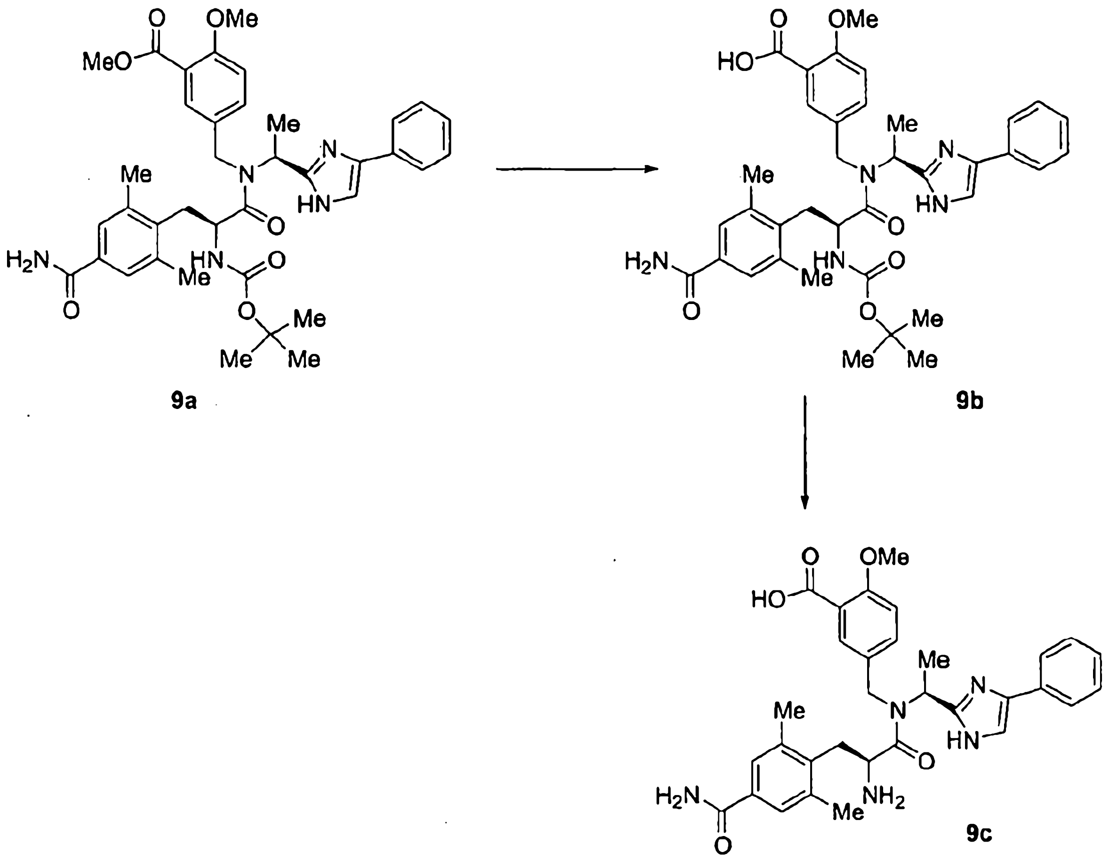
7.4 Hz), 3.65 (3H, s), 4.57-4.59 (1H, m), 5.14 (1H, d, *J* = 8.6 Hz), 7.75 (2H, s); MS(ES+) (relative intensity): 251.9 (100) (M-Boc)+.

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%); ^{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) $(M\text{-}Boc)^+$.

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%); ^{1}H 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-1*H*-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid



9a 9b 9c

A. **2-Methoxy-5-{[1-(4-phenyl-1*H*-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-1*H*-imidazol-2-yl)-ethylamino]-methyl}-benzoic acid methyl ester was prepared.

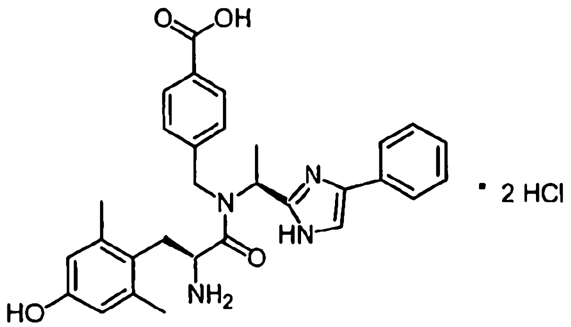
B. **5-({[2-*tert*-Butoxycarbonylmethyl-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic acid methyl ester.** Using the procedure of Example 1 for the conversion of Cpd **1d** to Cpd **1e**, substituting 2-methoxy-5-{[1-(4-phenyl-1*H*-imidazol-2-yl)-ethylamino]-methyl}-benzoic 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-1*H*-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-1*H*-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 $LiOH \cdot H_2O$/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 x 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-1*H*-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-1*H*-imidazol-2-yl)-ethyl]-amino}-methyl)-2-methoxy-benzoic**

acid. A portion of Cpd **9b** (0.27g, 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 (@214nm; 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-1*H*-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-1*H*-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-1 *H*-imidazol-2-yl)-ethyl]-amino}-methyl)-benzoic acid methyl ester.** 4-{[1-(4-phenyl-1*H*-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-1 *H*-imidazol-2-yl)-ethyl]-amino}-methyl)-benzoic acid.** A solution of

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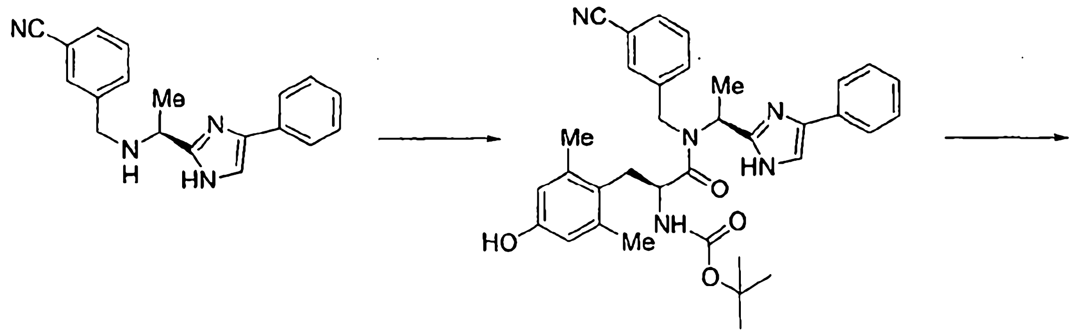
4-({[2-amino-3-(4-hydroxy-2,6-dimethyl-phenyl)-propionyl]-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-amino}-methyl)-benzoic acid methyl ester (TFA salt), (0.043 g, 0.067 mmol) in 5 mL of THF was cooled in an ice bath. A cold (5-10°C) 3M aqueous solution of LiOH (5 mL) was added and the reaction mixture 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-1 *H*-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-1 *H*-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-1*H*-imidazol-2-yl)-ethyl]-amino}-methyl)-benzamide



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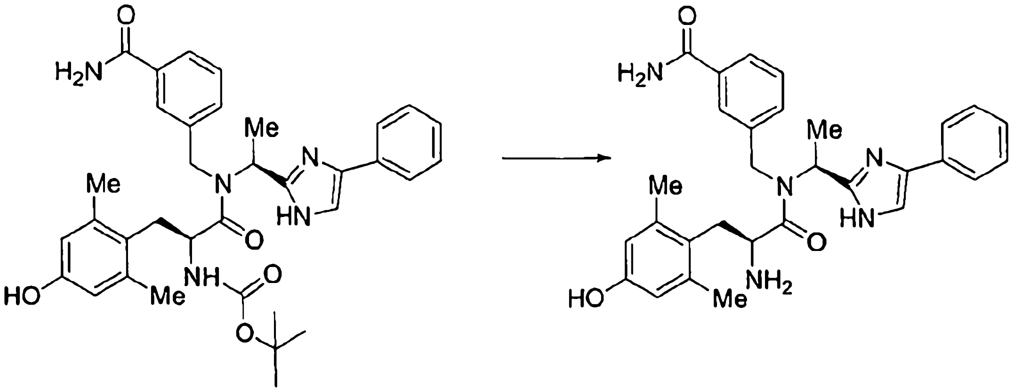

A. **3-{[1-(4-phenyl-1*H*-imidazol-2-yl)-ethylamino]-methyl}-benzonitrile.** Using the procedure described for Example 3, substituting 3-formyl-benzonitrile for 3,4-dimethoxybenzaldehyde, the product was prepared.

B. **[1-{(3-Cyano-benzyl)-[1-(4-phenyl-1*H*-imidazol-2-yl)-ethyl]-carbamoyl}-2-(4-hydroxy-2,6-dimethyl-phenyl)-ethyl]-carbamic acid *tert*-butyl ester.** 3-{[1-(4-phenyl-1*H*-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-1 *H*-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-1 *H*-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-1 *H*-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):

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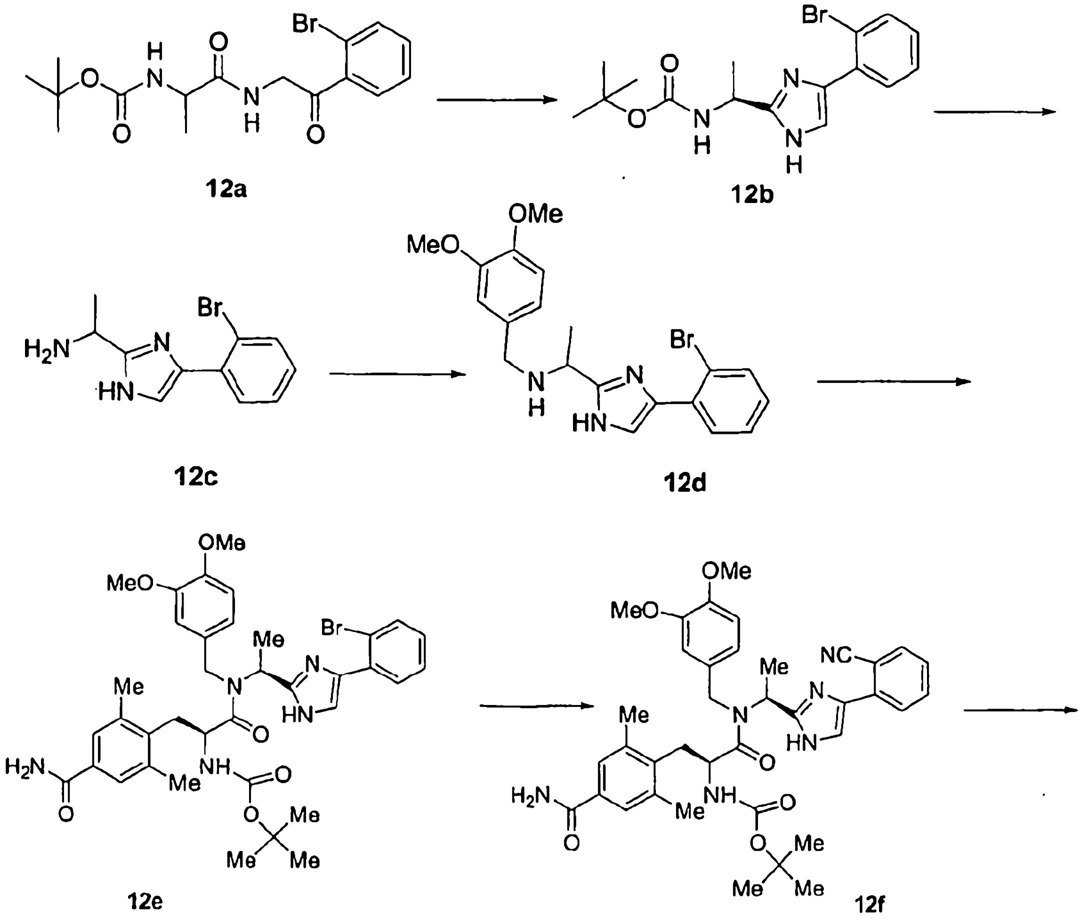
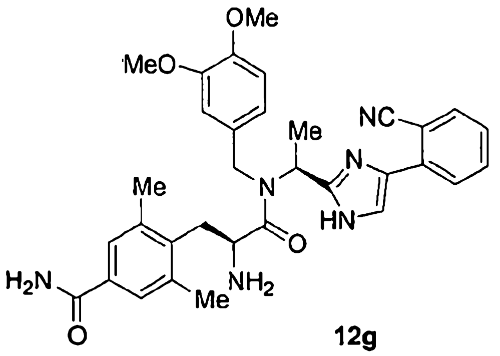
612.5 (100) (M+1). This sample was of sufficient quality to use in the next reaction without further purification.

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

<u>Example 12</u>

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





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)-1*H*-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)-1*H*-imidazol-2-yl]-ethylamine.** Using the procedure described for the conversion of Cpd **1e** to **1f**, Compound **12c** was prepared.

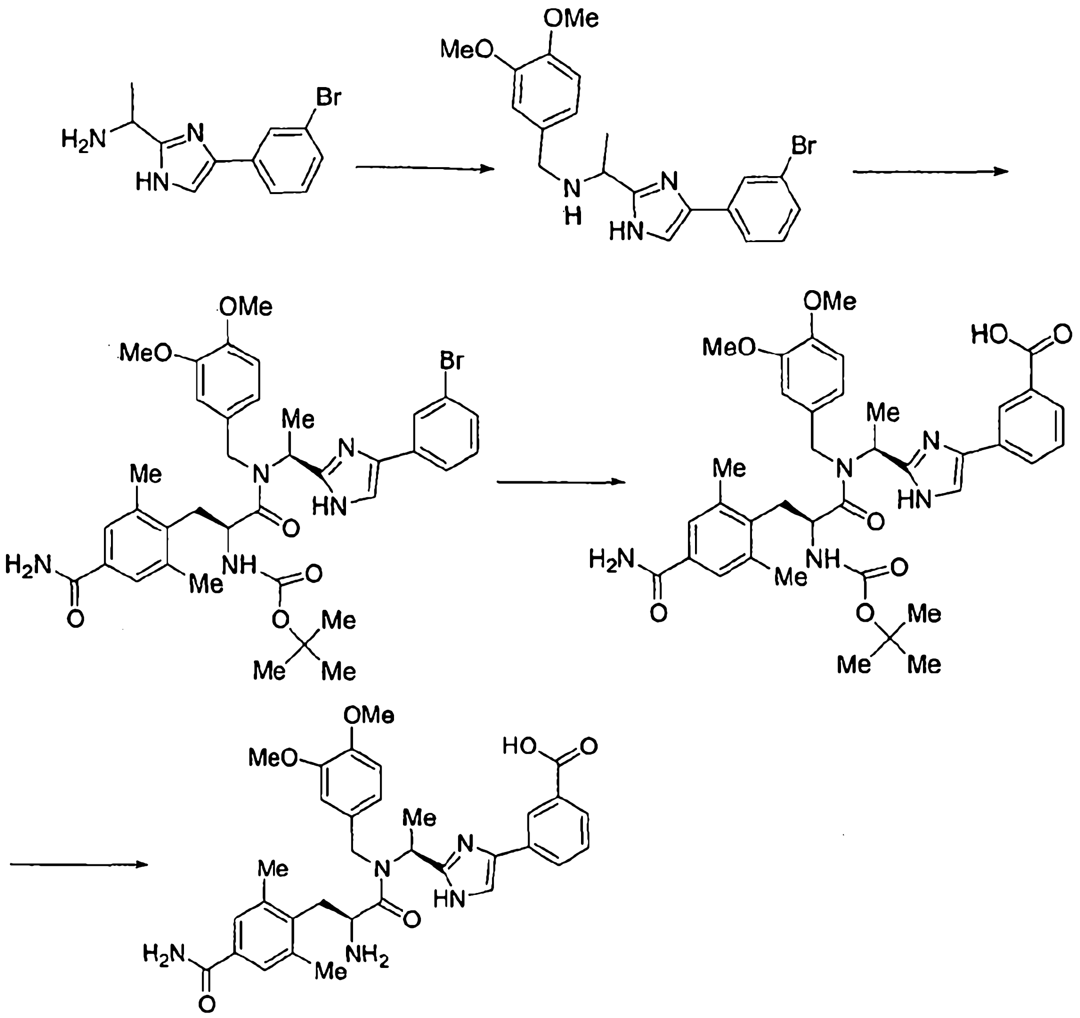
D. **[1-[{1-[4-(2-Bromo-phenyl)-1*H*-imidazol-2-yl]-ethyl}-(3,4-dimethoxy-benzyl)-carbamoyl]-2-(4-carbamoyl-2,6-dimethyl-phenyl)-ethyl]-carbamic acid *tert*-butyl ester.** Using the procedure described in Example 9, Step D, and substituting 1-[4-(4-bromo-phenyl)-1*H*-imidazol-2-yl]-ethylamine for 1-(4-phenyl-1*H*-imidazol-2-yl)-ethylamine,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



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

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

C. **[1-[{1-[4-(3-Bromo-phenyl)-1*H*-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)-1*H*-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}-1*H*-imidazol-4-yl)-benzoic acid.** To a solution of [1-[{1-[4-(3-bromo-phenyl)-1*H*-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 (5mL) 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 (4x). 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}-1*H*-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}-1*H*-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.

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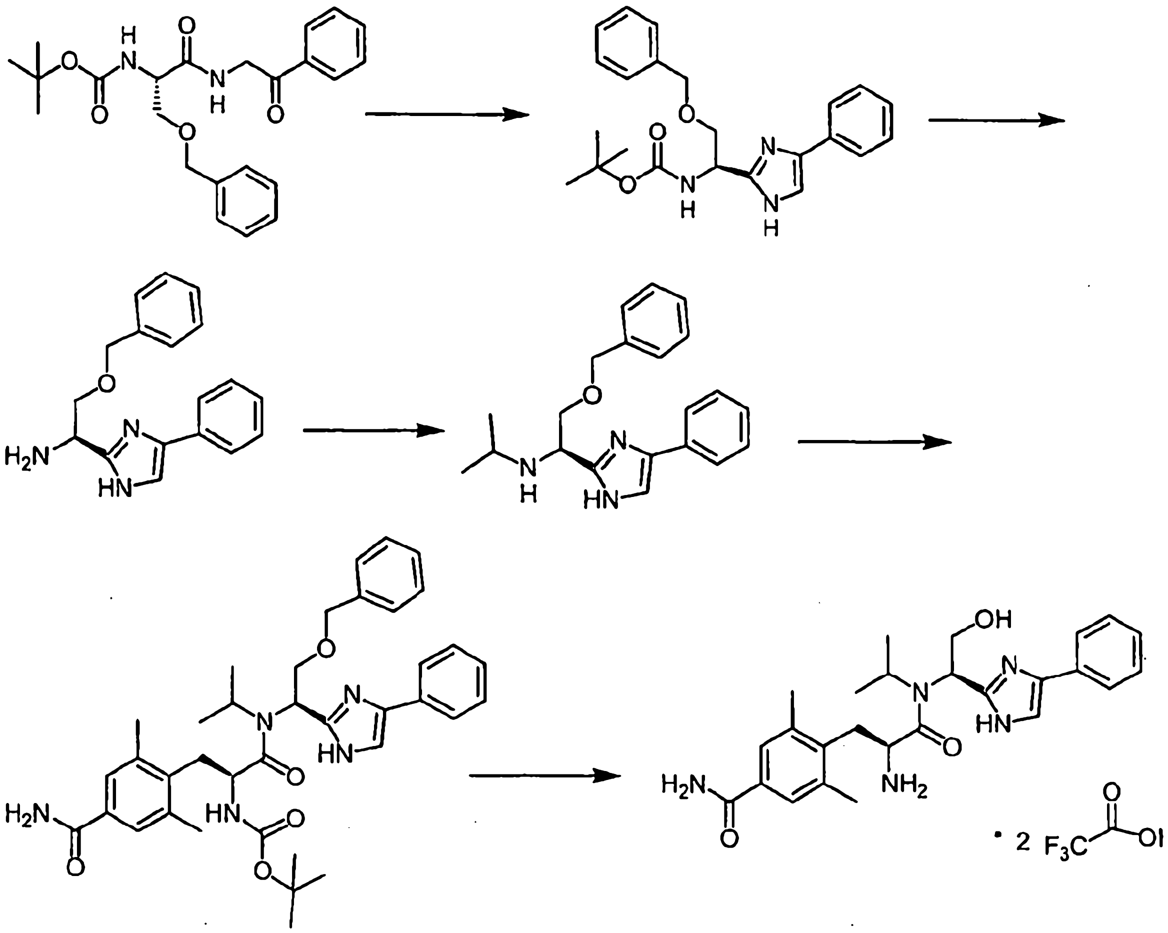
Example 14

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



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-1*H*-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-1*H*-imidazol-2-yl-ethylamine.** [2-benzyloxy-1-(4-phenyl-1*H*-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-1*H*-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-1*H*-imidazol-2-yl-ethylamine was converted to the product.

E. **[1-{[2-Benzyloxy-1-(4-phenyl-1*H*-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-1*H*-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-1 *H*-imidazol-2-yl)-ethyl]-isopropyl-carbamoyl}-ethyl)-3,5-dimethyl-benzamide (TFA salt).** A solution of [1-{[2-benzyloxy-1-(4-phenyl-1*H*-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

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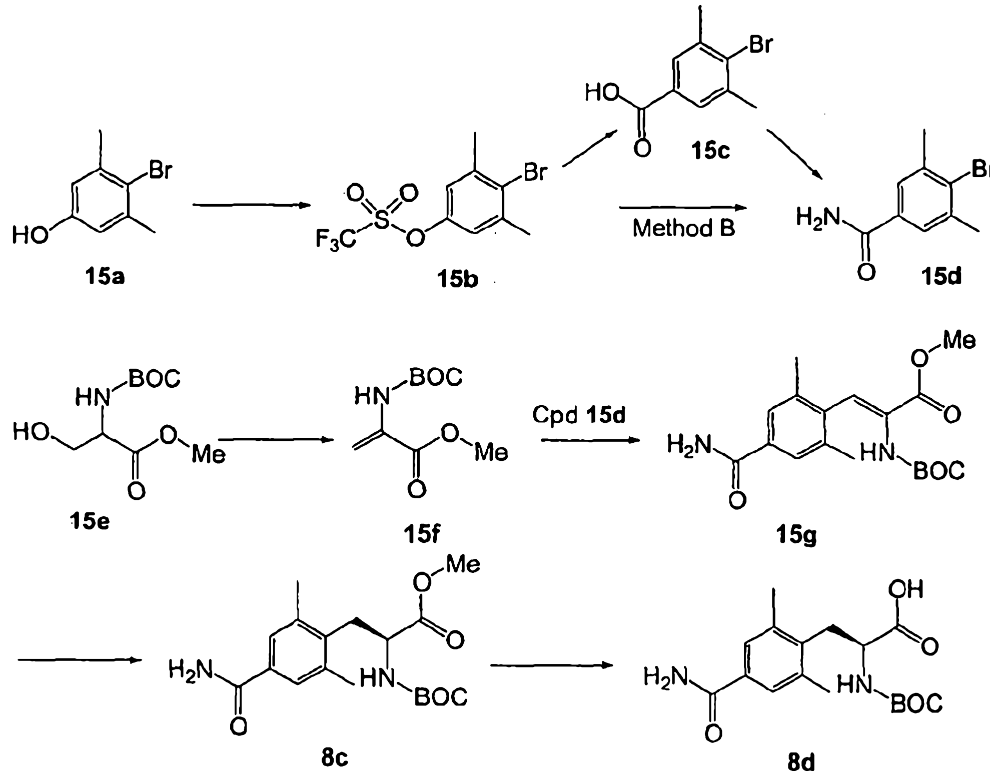
concentrated *in vacuo* to obtain 0.488 g of orange residue that was subjected to reverse phase HPLC (water/ acetonitrile / 0.1% TFA). The fractions of interest were combined and the sample was lyophilized to afford 0.150 g (59%) of 4-(2-amino-2-{[2-hydroxy-1-(4-phenyl-1 *H*-imidazol-2-yl)-ethyl]-isopropyl-carbamoyl}-ethyl)-3,5-dimethyl-benzamide (TFA salt) as a white powder (HPLC: 99% @ 254 nm and 100% @ 214 nm). MS (ES^+) (relative intensity): 464.1 (100) (M+1).

<u>Example 15</u>

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



A. **Trifluoromethanesulfonic acid 4-bromo-3,5-dimethyl-phenyl 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

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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 (2x), brine, and then dried over $MgSO_4$. Filtration and evaporation to dryness afforded Compound **15b** (5.30 g, 95%) as a colorless oil. ^1H 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 chramotagraphy (eluent: EtOAc) to give the Compound **15d** (2.90 g, 65% for 2 steps) as an off-white solid. ^1H 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 2N H_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. ^1H 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:

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EtOAc:hexane~1:1 to EtOAc only) to give Compound **15g** (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 **15g** (0.56 g, 1.6 mmol) in degassed MeOH (80 mL) was added $[Rh(cod)(R,R\text{-DIPAMP})]^+BF_4^-$ 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. [1]H 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) $(M\text{-Boc})^+$.

<u>Example 16</u>

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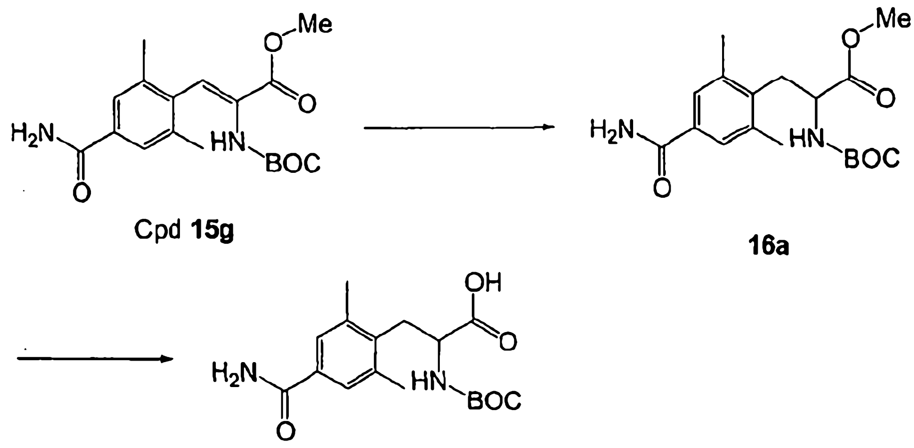
Racemic 2-*tert*-Butoxycarbonylamino-3-(4-carbamoyl-2,6-dimethyl-phenyl)-propionic acid



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 **15g** (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 ^{1}H 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

Cpd	Theoretical MW	Measured MW (MH^+)
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

Cpd	Theoretical MW	Measured MW (MH^+)
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
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

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Cpd	Theoretical MW	Measured MW (MH^+)
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

Cpd	Theoretical MW	Measured MW (MH^+)
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

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Cpd	Theoretical MW	Measured MW (MH^+)
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
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

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Cpd	Theoretical MW	Measured MW (MH$^+$)
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

Cpd	Theoretical MW	Measured MW (MH$^+$)
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
213	350.2	351.1

Cpd	Theoretical MW	Measured MW (MH^+)
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

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Cpd	Theoretical MW	Measured MW (MH^+)
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

Cpd	Theoretical MW	Measured MW (MH+)
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
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

Cpd	Theoretical MW	Measured MW (MH^+)
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 x 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 x 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 1a

Rat Brain Delta Opioid Receptor Binding Assay-Version 1a

Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) 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 x 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 x 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 x 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, NY) 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 x 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)	Cpd	r Ki δ * (nM)	r Ki δ * Ver. 1a (nM)	r Ki μ * (nM)

Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)	Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
1	13.2		1.1	146			
2				147			
3				149			
4	11, 17		2.41	150			
5	630, 183		1.19	151			
6	1.7			152			
7				153			
8	0.43, 0.15		0.51	154			
9	0.11		0.16	155			
10				156			
11	0.54		0.23	157			
12	0.08			158			
13				159			
14	0.36			160			
15				161			
16				162			
17	60		0.22	163	4.51		0.03
18	0.38-14.4		0.75, 1.1	164	120		0.38
19				165	23.6		0.07
20				166	5.58, 12.03		0.03, 0.07
21				167	10000		3.15
22				168	8867		5322
23				169	10000		853
24				170	32.6		0.48
25				171	10000		141
26				172	10000		150
27				173	5069		45.7
28				174			
29	28		25	175	166		3.60
30				176	10000		156
31				177	255		13.4

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Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)	Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
32				178	104		0.6
33				179	10000		7116
34				180	5221		1209
35				181	341		1.3
36				182	1859		7
37				183	604		4
38				184	10000		19.5
39				185	182		6716
40				186	515		5314
41				187	5198		121
42				188	541		307
43				189	360		277
44				190	13.8		2.61
45				191	727.3		189
46				192	7.64		0.09
47				193	182.1		21.1
48		0.24	0.14	194	14.8		0.06
49				195	306.2		9.29
50	0.58		1.68	196			
51				197	4.27		0.9
52				198	5178		152
53				199	26.3		0.3
54				202	31.5		5.9
55				203	49.3		29.1
56				204			
57				205	4.44		0.14
58				206	5.8		0.2
59				207	5.3, 5.37, 14.7		0.05, 0.08, 0.1
60				208	33		1.3
61				209	708		17
62				210	1862		420.3

Cpd	r Ki δ * (nM)	r Ki δ * Ver. 1a (nM)	r Ki μ * (nM)	Cpd	r Ki δ * (nM)	r Ki δ * Ver. 1a (nM)	r Ki μ * (nM)
63				211	180		5.9
64				212	1278		103
65				213	5658		1263
66				214	308		44
67				215	126		0.43
68				216	1.14		0.04
69				217	5.4		1.08
70				218	1.45		0.03
71				219	87.83		0.87
72				220	6921		157.2
73				221	9.58		0.36
74				222	394		91.2
75	0.66		0.51	223	2.6		0.87
76				224	1.41		0.03
77				225	112		0.73
78				226	48		
79				227	0.08, 0.46		0.96
80				228	27.8		0.35
81				229			
82				230	10		5
83				231	1070		6.19
84				239	0.1		0.44
85				242	0.18		0.59
86				246	0.035		0.15
87				247	0.4		0.61
88				248	0.44		0.11
89				249	0.18		0.12
90				250	0.21		0.06
91				249	0.18		0.12
92				250	0.21		0.06
93				251	0.26		0.08
94				249	0.18		0.12
95				250	0.21		0.06

Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)	Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
96				251	0.26		0.08
97				256	3.82		7.08
98				257		14.0	1.22
99				260	0.13		0.24
100				261	8.01		0.79
101				262	17.5		1.1
102				266			
103				267	0.46		1.53
104				268			
105				269	0.61	6.24	0.37
106				270	1.03	4.47	1.37
107				271	12.2		0.27
108				272	15.6		1.1
109				273	1140		754
110				274			
111				275	0.47		0.69
112				276	115		47
113				277	0.14		0.44
114	12		0.26	278	49		12
115				279	5.2		0.137
116				280	32		3
117				281	721		399
118				282	907		185
119				283	6735		3572
120				284	1526		1033
121				285	2897		1868
122				286	0.11		0.05
123				287	0.14		0.13
124				288	0.17		0.43
125				288	0.17		0.43
126				289	0.1, 3.8		0.25
127				290	0.69		0.43
128				291	0.12		0.47
129				292	100		0.65
130				293	3175		646
131				295	3.95		0.18

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Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)	Cpd	r Ki δ* (nM)	r Ki δ* Ver. 1a (nM)	r Ki μ* (nM)
132				296	2.2		0.49
133				297	44		0.11
134				298	44		0.3
135				299	1.16		0.44
136				300	0.29		0.09
137				301	0.76		0.09
138				303		24.5	3.87
139				304		119	161
140				305		1.24	0.2
141				306		0.18	0.9
142				307		0.07	0.4
143				308		0.48	1.2
144				318	1220		357
145							

* 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 6X 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 6X 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 6X the desired final

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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 6X 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)	Cpd	hKi δ* (nM)	h Ki µ* (nM)
1		3.6	**115**	321	68
2		2.9	**116**	30.3	0.54
3		13	**117**	118	0.24
4		5.5	**118**	316, 212	1.04
5		3.9	**119**	>10,000	185
6		2	**120**	740	20.8
7		6.8	**121**	182	25.3
8		2.5, 4.4	**122**	107	12.8
9		10.9	**123**	84	47

Cpd	hKi δ^* (nM)	hKi μ^* (nM)	Cpd	hKi δ^* (nM)	h Ki μ^* (nM)
10		15.5	**124**	1279	1.7
11		5.1	**125**	237	8.6
12		4.1	**126**	164	7.8
13		4.8	**127**	710	47
14		4.7	**128**		58
15		285	**129**		25.3
16		16	**130**	712	1.6
17		2.2	**131**	675	3.1
18		1.7	**132**		166
19		18.2	**133**	108	11.5
20		63	**134**	463	121
21		37.6	**135**	1040	7
22		~200	**136**	1607	726
23		34.3	**137**		445
24		9.3	**138**	1183	104
26		17	**139**	1263	58
27		30	**140**	985	79
28		44	**141**	252	52
29		38	**142**	454	8.2
30		34	**143**	69	1.6
31		19	**144**	251	1.3
32		6.8	**145**	267	
33		6.9	**146**	71	
34		19	**147**	241	
35		2.8	**149**	408	
36		5.6	**150**	992	
37		183	**151**	1295	
38		19	**152**	>10,000	
39		0.9	**153**	>10,000	
40		152	**154**	>10,000	1
41		1.6	**155**	345	
42		5.8	**156**	380	0.59

Cpd	hKi δ* (nM)	hKi μ* (nM)
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	65.3
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

Cpd	hKi δ* (nM)	h Ki μ* (nM)
157	>10,000	2.2
158	>10,000	0.23
159	400	8.6
160	>10000	>1000
161	>10000	>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

Cpd	hKi δ * (nM)	hKi μ * (nM)	Cpd	hKi δ * (nM)	h Ki μ * (nM)
75	8.5	2.6	**214**		29
76	43.1	1.6	**215**		1.5
77	13.5	1.8	**216**		
78	28.9	2.4	**217**	506	
79	11.5	1.7	**218**	189	3.92
80	0.95	1.09	**219**		16.2
81	15.7	1.7	**220**		377
82	46	2.39	**221**		0.42
83	48	4.67	**222**		185
84	9.6	1.1	**223**		
85	1175	5.4	**224**	81.3	0.65
86	400	1	**225**		1.4
87	38.9	12.6	**226**		7.91
88	16.2	5.8	**227**		1.92
89	19.3	9.2	**228**		15.9
90	6.6	0.7	**229**		12
91	15	4.8	**231**		28
92	5.4	0.25	**239**		
93	9.5	0.9	**242**		2.35
94	403	4.1	**246**		5.63
95	278	7.8	**256**		2
96	14.6	9.7	**257**		3.4
97	6.3	19.2	**260**		0.58
98	54	48	**261**		2.58, 1.3
99	19.3	16	**262**		3.24
100	88	20	**266**		69
101	47	24	**267**		6.88
102	5.2	3.5	**268**		5.79
103	9.7	23	**269**		21.5
104	484	100	**270**		3.27
105	742	410	**271**		15.5
106	279	150	**272**		1.93
107	584	2.95	**273**		325
108	43.3	23.5	**274**		>1000

Cpd	hKi δ * (nM)	hKi μ * (nM)
109	77	8.2
110	1402	191
111	307	6.4
112	135	9.5
113		16
114	49	1.39

Cpd	hKi δ * (nM)	h Ki μ * (nM)
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

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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 1μM SNC80 in presence of test compound) x 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.

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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 TopCount. The following parameters were calculated:

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

% Inhibition =

(% stimulation by 1 μM SNC80 – %stimulation by 1 μM SNC80 in presence of test compound) x 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

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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				
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

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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)
192	76					383.00	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					582.00	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				
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		

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)
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 I 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 x 20 cm deep x 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 x 20 cm deep x 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.

<u>Table X</u>

		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

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Cpd No.	dose (mg/kg)	Fecal Output (# pellets) control	NES	cpd	NES % ctrl	cpd % control	cpd % NES
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
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
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

Cpd No.	# of pellets: control	# of pellets: NES	NES (% ctrl)	Compound (mg) 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 No.	Compound (% control) 0.3	0.5	1.0	3.0	5.0	6.0	10.0	30.0	Compound (% NES) 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. ~30g. Procedure: Mice were housed in LAM under 12h/12h 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/10g 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. ~30g. Mice were housed under 12h/12h 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)} x 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

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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 (Figure 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 (Figure 2 and Figure 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 (Nov, 1996).

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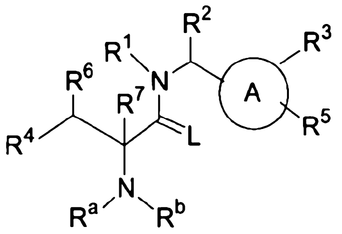
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A compound of Formula (I)



Formula (I)

wherein:

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

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

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

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

$_{6}$)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;

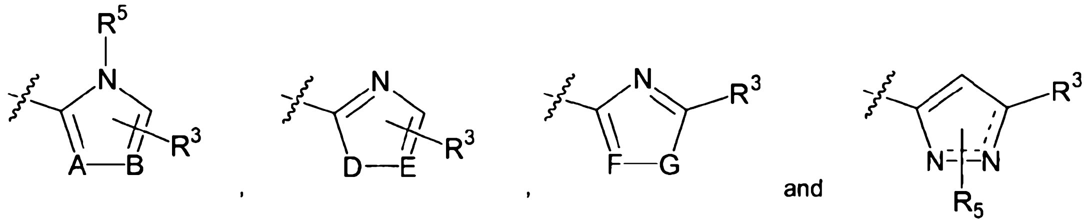
furthermore, wherein the aryl and heteroaryl portion of the R^1 substituents aryl(C_{1-6})alkyl and heteroaryl(C_{1-6})alkyl, are optionally substituted with one to three R^{11} substituents independently selected from the groupconsisting of C_{1-6}alkyl; hydroxy(C_{1-6})alkyl; C_{1-6}alkoxy; C_{6-10}aryl(C_{1-6})alkyl; 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 selected from the group consisting of ring system **a-1**, **a-2**, **a-3**, and **a-4**, optionally substituted with R^3 and R^5;



a-1 a-2 a-3 a-4

wherein

A-B is selected from the group consisting of 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 $C_{1\text{-}6}$alkyl, aryl, aryl($C_{1\text{-}6}$)alkyl, aryl($C_{2\text{-}6}$)alkenyl, aryl($C_{2\text{-}6}$)alkynyl, heteroaryl, heteroaryl($C_{1\text{-}6}$)alkyl, heteroaryl($C_{2\text{-}6}$)alkenyl, heteroaryl($C_{2\text{-}6}$)alkynyl, amino, $C_{1\text{-}6}$alkylamino, ($C_{1\text{-}6}$alkyl)$_2$amino, arylamino, heteroarylamino, aryloxy, heteroaryloxy, trifluoromethyl, and halogen;

wherein the aryl , heteroaryl, and the aryl and heteroaryl of aryl($C_{1\text{-}6}$)alkyl, aryl($C_{2\text{-}6}$)alkenyl, aryl($C_{2\text{-}6}$)alkynyl, heteroaryl($C_{1\text{-}6}$)alkyl, heteroaryl($C_{2\text{-}6}$)alkenyl, heteroaryl($C_{2\text{-}6}$)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 $C_{1\text{-}6}$alkyl, hydroxy($C_{1\text{-}6}$)alkyl, $C_{1\text{-}6}$alkoxy, $C_{6\text{-}10}$aryl($C_{1\text{-}6}$)alkyl, $C_{6\text{-}10}$aryl($C_{1\text{-}6}$)alkoxy, $C_{6\text{-}10}$aryl, $C_{6\text{-}10}$aryloxy, heteroaryl($C_{1\text{-}6}$)alkyl, heteroaryl($C_{1\text{-}6}$)alkoxy, heteroaryl, heteroaryloxy, $C_{6\text{-}10}$arylamino, heteroarylamino, amino, $C_{1\text{-}6}$alkylamino, ($C_{1\text{-}6}$alkyl)$_2$amino, carboxy($C_{1\text{-}6}$)alkylamino, carboxy, $C_{1\text{-}6}$alkylcarbonyl, $C_{1\text{-}6}$alkoxycarbonyl, $C_{1\text{-}6}$alkylcarbonylamino, aminocarbonyl, $C_{1\text{-}6}$alkylaminocarbonyl, ($C_{1\text{-}6}$alkyl)$_2$aminocarbonyl, carboxy($C_{1\text{-}6}$)alkylaminocarbonyl, cyano, halogen, trifluoromethyl, trifluoromethoxy, hydroxy, $C_{1\text{-}6}$alkylsulfonyl, and $C_{1\text{-}6}$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 $C_{6\text{-}10}$aryl($C_{1\text{-}6}$)alkyl, $C_{6\text{-}10}$aryl($C_{1\text{-}6}$)alkoxy, $C_{6\text{-}10}$aryl, $C_{6\text{-}10}$aryloxy, heteroaryl($C_{1\text{-}6}$)alkyl, heteroaryl($C_{1\text{-}6}$)alkoxy, heteroaryl, heteroaryloxy, $C_{6\text{-}10}$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 or C_{1-6}alkyl;

and pharmaceutically acceptable enantiomers, diastereomers, racemates, and salts thereof, with the proviso that the compound of Formula (I) is other than:

(a) a compound wherein R^1=H or methyl; R^2=CH_2-phenyl or CH_2-naphthyl; A=ring system a-2 wherein D-E=O-N; R^3=methyl; R^4=naphthyl; R^5=absent; R^6=R^7=H; R^a=H or methyl; R^b=H, methyl or alkoxycarbonyl; and L=O;

(b) a compound wherein R^1=H; R^2=methyl; A=ring system a-1 wherein A-B=N-N; R^3=hydroxyl substituted phenyl; R^4=phenyl; R^5= R^6=R^7=H; R^a=H; R^b=alkoxycarbonyl; and L=O.

2. A compound according to 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.

3. A compound according to 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

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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.

4. A compound according to 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.

5. A compound according to claim 1, 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.

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6. A compound according to 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.

7. A compound according to claim 1, wherein R^2 is a substituent selected from the group consisting of hydrogen and C_{1-4}alkyl.

8. A compound according to claim 1, wherein R^2 is hydrogen or methyl.

9. A compound according to claim 1, wherein ring A is a-1.

10. A compound according to claim 1, wherein A-B of a-1 is O-N.

11. A compound according to 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.

12. A compound according to 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.

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13. A compound according to 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.

14. A compound according to claim 1, wherein at least one R^3 substituent is phenyl.

15. A compound according to 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

16. A compound according to claim 1, wherein R^4 is C_{6-10}aryl optionally substituted with one to three R^{41} substituents independently selected from the groupconsisting 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.

17. A compound according to 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,

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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.

18. A compound according to 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.

19. A compound according to 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.

20. A compound according to 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.

21. A compound according to claim 1, wherein R^5 is hydrogen or methyl.

22. A compound according to claim 1, wherein R^5 is hydrogen.

23. A compound according to claim 1, wherein R^6 is hydrogen or methyl.

24. A compound according to claim 1, wherein R^6 is hydrogen.

25. A compound according to claim 1, wherein R^7 is hydrogen or methyl.

26. A compound according to claim 1, wherein R^7 is hydrogen.

27. A compound according to 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 five to seven membered monocyclic ring.

28. A compound according to claim 1, wherein R^a and R^b are independently hydrogen or methyl.

29. A compound according to claim 1, wherein R^a and R^b are each hydrogen.

30. A compound according to claim 1, wherein L is O.

31. A compound according to claim 1, that are present in their RR, SS, RS, and SR configurations.

32. A compound according to claim 1, in their S,S configuration.

33. A composition comprising the compound of claim 1 and a pharmaceutically acceptable carrier.

34. A method of making a composition comprising admixing the compound of claim 1 and a pharmaceutically acceptable carrier.

35. A method for treating or ameliorating a δ or μ-opioid receptor mediated disorder in a subject in need thereof comprising administerin to the subject a therapeutically effective amount of the compound of claim 1.

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36. Use of a compound as defined according to claim 1, in the preparation of a medicament for treating or ameliorating a δ or μ-opioid receptor mediated disorder in a subject.

Dated this 9th day of January 2014
Shelston IP
Attorneys for: Janssen Pharmaceutica, N.V.

2012202459 27 Apr 2012

Figure 1

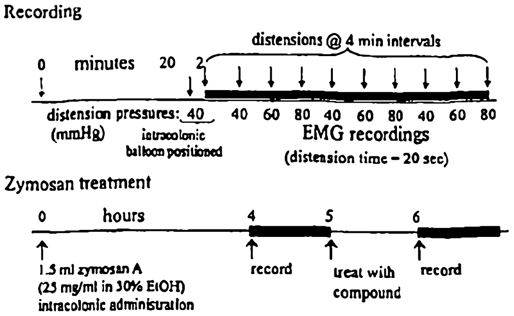

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Figure 2.

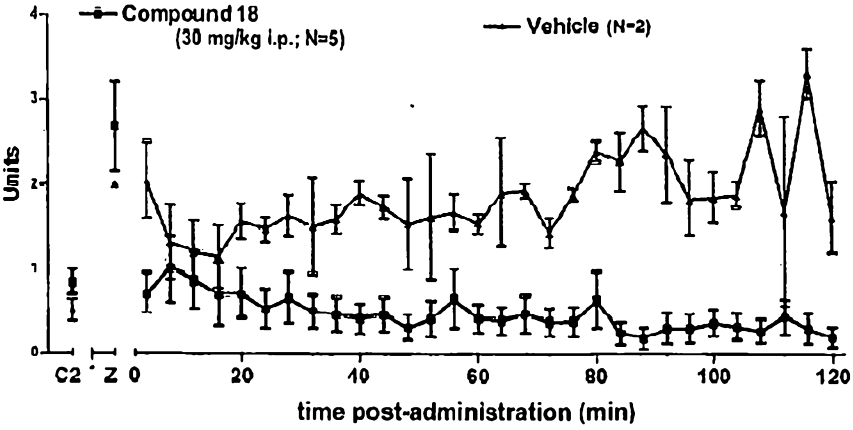

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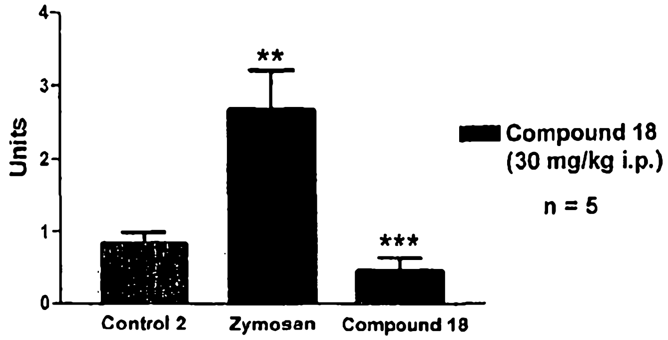
Figure 3.



** = P < 0.01 vs. Control 2

*** = P < 0.001 vs. Zymosan