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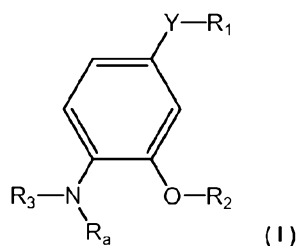
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(54) Title: 4-SUBSTITUTED-2-PHENOXY-PHENYLAMINE DELTA OPIOID RECEPTOR MODULATORS



(57) Abstract: Disclosed are compounds, compositions and methods for treating various diseases, syndromes, conditions and disorders, including pain. Such compounds are represented by Formula I as follows: wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>a</sub>, and Y are defined herein.

**4-SUBSTITUTED-2-PHENOXY-PHENYLAMINE  
DELTA OPIOID RECEPTOR MODULATORS**

**5 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.

**10 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 term "opiate" has been used to designate pharmacologically active  
15 alkaloids derived from opium, e.g., morphine, codeine, and many semi-synthetic congeners of morphine. After the isolation of peptide compounds with morphine-like actions, the term opioid was introduced to refer generically to all drugs with morphine-like actions. Included among opioids are various peptides that exhibit morphine-like activity, such as endorphins, enkephalins and dynorphins. However,  
20 some sources use the term "opiate" in a generic sense, and in such contexts, opiate and opioid are interchangeable. Additionally, the term opioid has been used to refer to antagonists of morphine-like drugs as well as to characterize receptors or binding sites that combine with such agents.

Opioids are generally employed as analgesics, but they may have many other  
25 pharmacological effects as well. Morphine and related opioids produce certain of their major effects on the central nervous and digestive systems. The effects are diverse, including analgesia, drowsiness, mood changes, respiratory depression, dizziness, mental clouding, dysphoria, pruritus, increased pressure in the biliary tract, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and  
30 autonomic nervous systems.

When therapeutic doses of morphine are given to patients with pain, they report that the pain is less intense, less discomforting, or entirely gone. In addition to experiencing relief of distress, some patients experience euphoria. However, when morphine in a selected pain-relieving dose is given to a pain-free individual, the experience is not always pleasant; nausea is common, and vomiting may also occur. Drowsiness, inability to concentrate, difficulty in mentation, apathy, lessened physical activity, reduced visual acuity, and lethargy may ensue.

Two distinct classes of opioid molecules can bind opioid receptors: the opioid peptides (e.g., the enkephalins, dynorphins, and endorphins) and the alkaloid opiates (e.g., morphine, etorphine, diprenorphine and naloxone). Subsequent to the initial demonstration of opiate binding sites (Pert, C. B. and Snyder, S. H., *Science* (1973) 179:1011-1014), the differential pharmacological and physiological effects of both opioid peptide analogues and alkaloid opiates served to delineate multiple opioid receptors. Accordingly, three molecularly and pharmacologically distinct opioid receptor types have been described: delta, kappa and mu. Furthermore, each type is believed to have sub-types (Wollemann, M., *J Neurochem* (1990) 54:1095-1101; Lord, J. A., et al., *Nature* (1977) 267:495-499).

All three of these opioid receptor types appear to share the same functional mechanisms at a cellular level. For example, the opioid receptors cause inhibition of adenylate cyclase, and inhibition of neurotransmitter release via both potassium channel activation and inhibition of  $\text{Ca}^{2+}$  channels (Evans, C. J., In: *Biological Basis of Substance Abuse*, S. G. Korenman & J. D. Barchas, eds., Oxford University Press (in press); North, A. R., et al., *Proc Natl Acad Sci USA* (1990) 87:7025-29; Gross, R. A., et al., *Proc Natl Acad Sci USA* (1990) 87:7025-29; Sharma, S. K., et al., *Proc Natl Acad Sci USA* (1975) 72:3092-96). Although the functional mechanisms are the same, the behavioral manifestations of receptor-selective drugs differ greatly (Gilbert, P. E. & Martin, W. R., *J Pharmacol Exp Ther* (1976) 198:66-82). Such differences may be attributable in part to the anatomical location of the different receptors.

Delta receptors have a more discrete distribution within the mammalian CNS than either mu or kappa receptors, with high concentrations in the amygdaloid complex, striatum, substantia nigra, olfactory bulb, olfactory tubercles, hippocampal

formation, and the cerebral cortex (Mansour, A., et al., Trends in Neurosci (1988) 11:308-14). The rat cerebellum is remarkably devoid of opioid receptors including delta opioid receptors.

5 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.

There is a general need for new delta opioid receptor modulators as analgesics. There is a general need for delta opioid receptor selective agonists as analgesics having reduced side effects. There is also a general need for delta opioid receptor antagonists as immunosuppressants, antiinflammatory agents, agents for the treatment  
10 of neurological and psychiatric conditions, agents for the treatment of urological and reproductive conditions, medicaments for drug and alcohol abuse, agents for treating gastritis and diarrhea, cardiovascular agents and agents for the treatment of respiratory diseases, having relatively reduced side effects.

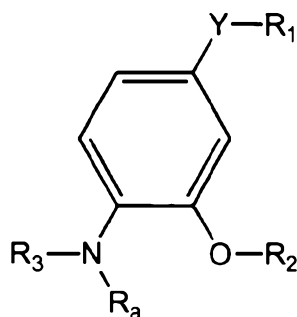
There is a general need for new opioid receptor modulators as analgesics.  
15 There is a general need for delta and mu opioid receptor agonists as analgesics having reduced side effects. There is a further general need for mu opioid receptor agonists as analgesics having reduced side effects for the treatment of pain, immune function, esophageal reflux, and cough. There is also a general need for delta opioid receptor agonists as analgesic agents, agents for the treatment of respiratory diseases,  
20 cardiovascular agents, agents for treating urological dysfunction, and agents for the treatment of neurological and psychiatric conditions. There is general need for dual delta opioid receptor/ mu opioid receptor agonists.

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  
25 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<sub>1</sub> is selected from the group consisting of

- i) phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, hydroxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, chloro, and fluoro; such that only one di(C<sub>1-4</sub>alkyl)aminocarbonyl is present;
  - ii) naphthyl;
  - iii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, hydroxy, fluoro, chloro, and cyano;
  - iv) pyrimidin-5-yl;
  - v) furanyl;
  - vi) thienyl;
  - vii) 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl; and
  - viii) di(C<sub>1-2</sub>alkyl)aminocarbonyl;
- with the proviso that when R<sub>1</sub> is 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, Y is a bond;
- Y is ethyl, vinyl, or a bond;
- or, Y is O when R<sub>1</sub> is an optionally substituted phenyl;

R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoro, chloro, cyano, trifluoromethoxy, and hydroxy;

or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl, di(C<sub>1-</sub>

5                   4alkyl)aminocarbonyl, C<sub>1-4</sub>alkoxycarbonyl, or carboxy substituent;

R<sub>3</sub> is selected from the group consisting of

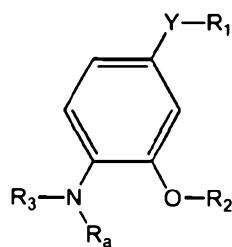
- i) 3-amino-cyclohexyl;
- ii) 4-amino-cyclohexyl;
- iii) piperidin-3-yl;
- 10   iv) piperidin-4-yl;
- v) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one to two fluoro substituents;
- vi) azetidin-3-ylmethyl;
- vii) 2-(N-methylamino)ethyl;
- 15   viii) 3-hydroxy-2-amino-propyl;
- ix) piperidin-3-ylmethyl;
- x) 1-azabicyclo[2.2.2]octan-3-yl; and
- xi) 8-azabicyclo[3.2.1]octan-3-yl;

20                   or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl optionally substituted with 4-C<sub>1-4</sub>alkyl;

R<sub>a</sub> is hydrogen, 2-(N-methylamino)ethyl, or C<sub>1-2</sub>alkyl optionally substituted with azetidin-3-yl;

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

According to a second 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

- i) phenyl optionally substituted with one to two substituents independently selected from the group consisting of  $C_{1-4}$ alkoxy,  $di(C_{1-4}$ alkyl)aminocarbonyl, and fluoro; such that only one  $di(C_{1-4}$ alkyl)aminocarbonyl is present;
- ii) naphthyl;
- iii) pyridinyl optionally substituted with one substituent selected from the group consisting of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylthio, fluoro, and cyano;
- iv) pyrimidin-5-yl;
- v) furanyl;
- vi) thienyl; and
- vii)  $di(C_{1-2}$ alkyl)aminocarbonyl;

Y is vinyl or a bond; or, Y is O when  $R_1$  is an optionally substituted phenyl;

$R_2$  is phenyl optionally substituted with one to two substituents independently selected from the group consisting of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, fluoro, chloro, and hydroxy;

or,  $R_2$  is phenyl substituted with one aminocarbonyl or  $di(C_{1-4}$ alkyl)aminocarbonyl substituent;

$R_3$  is selected from the group consisting of

- i) 3-amino-cyclohexyl;
- ii) 4-amino-cyclohexyl;
- iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one to two fluoro substituents; 2-(N-methylamino)ethyl; piperidin-3-ylmethyl; and
- iv) 1-azabicyclo[2.2.2]octan-3-yl;

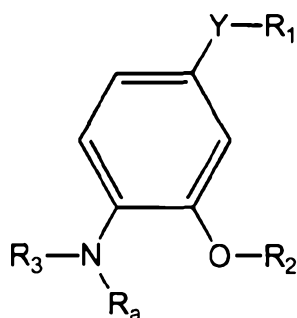
or,  $R_3$  is taken with  $R_a$  and the nitrogen atom to which they are both attached to form piperazinyl;

$R_a$  is hydrogen or  $C_{1-2}$ alkyl;



and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

According to a third aspect of the present invention there is provided a compound of Formula (I)



Formula (I)

wherein

R<sub>1</sub> is selected from the group consisting of

- i) phenyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, and fluoro;
- ii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
- iii) pyrimidin-5-yl; and
- iv) di(C<sub>1-2</sub>alkyl)aminocarbonyl;

Y is vinyl or a bond;

R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, and hydroxy;

or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl or di(C<sub>1-4</sub>alkyl)aminocarbonyl substituent;

R<sub>3</sub> is selected from the group consisting of

- i) 3-amino-cyclohexyl;
- ii) 4-amino-cyclohexyl;

iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at a carbon atom with one to two fluoro substituents;

iv) 2-(N-methylamino)ethyl;

v) piperidin-3-ylmethyl; and

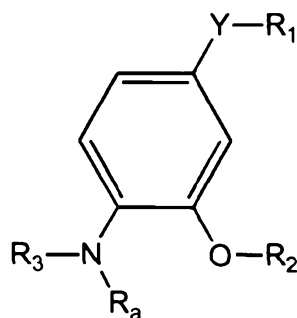
vi) 1-azabicyclo[2.2.2]octan-3-yl;

or,  $R_3$  is taken with  $R_a$  and the nitrogen atom to which they are both attached to form piperazinyl;

$R_a$  is hydrogen;

and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

According to a fourth 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

i) phenyl optionally substituted with one methoxy substituent;

ii) pyridinyl optionally substituted with one substituent selected from the group consisting of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylthio, fluoro, and cyano;

iii) pyrimidin-5-yl; and

iv) di( $C_{1-2}$ alkyl)aminocarbonyl;

Y is vinyl or a bond;

$R_2$  is phenyl optionally substituted with one substituent independently selected from the group consisting of methoxy, hydroxy, aminocarbonyl, and  $C_{1-4}$ alkylcarbonylamino;

5  $R_3$  is selected from the group consisting of

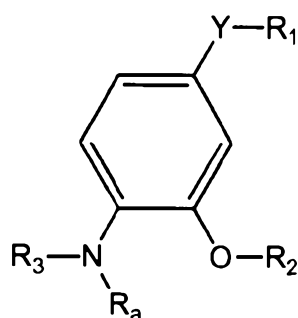
- i) 3-amino-cyclohexyl;
- ii) 4-amino-cyclohexyl;
- iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at a carbon atom with one fluoro substituent; and

10 or,  $R_3$  is taken with  $R_a$  and the nitrogen atom to which they are both attached to form piperazinyl;

$R_a$  is hydrogen;

and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

15 According to a fifth aspect of the present invention there is provided a compound of Formula (I)



Formula (I)

selected from the group consisting of

20 a compound wherein  $R_1$  is 2-(*N,N*-diethylaminocarbonyl),  $Y$  is (*E*)-vinyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)

a compound wherein  $R_1$  is 2-(*N,N*-diethylaminocarbonyl),  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)

25 a compound wherein  $R_1$  is 2-(4-methoxy-phenyl),  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)

a compound wherein  $R_1$  is 2-(3-methoxy-phenyl),  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)

- a compound wherein  $R_1$  is 2-phenyl, Y is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is 2-(4-fluoro-phenyl), Y is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 5 a compound wherein  $R_1$  is 2-(3-fluoro-phenyl), Y is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is 2-[3-(*N,N*-diethylaminocarbonyl)phenyl], Y is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 10 a compound wherein  $R_1$  is *N,N*-diethylaminocarbonyl, Y is a bond,  $R_2$  is phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is *N,N*-diethylaminocarbonyl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 15 a compound wherein  $R_1$  is *N,N*-diethylaminocarbonyl, Y is a bond,  $R_2$  is 2-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-cyano-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 3-cyano-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 20 a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 3-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-fluoro-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 25 a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-trifluoromethoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 2,6-dichloro-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 30 a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is 2-(*N*-methylamino)ethyl, and  $R_a$  is H;
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-methoxycarbonyl-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)

- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 3-methoxycarbonyl-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 2,4-dichloro-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 5 a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is piperidin-4-yl, and  $R_a$  is H;
- a compound wherein  $R_1$  is 5-cyano-pyridin-3-yl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is 4-fluoro-pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*,4*R*)
- 10 a compound wherein  $R_1$  is 5-fluoro-pyridin-3-yl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is 4-fluoro-pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*,4*R*)
- a compound wherein  $R_1$  is 5-methylthio-pyridin-3-yl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is 4-fluoro-pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*,4*R*)
- a compound wherein  $R_1$  is 5-methoxy-pyridin-3-yl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is 4-fluoro-pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*,4*R*)
- 15 a compound wherein  $R_1$  is 5-methyl-pyridin-3-yl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is 4-fluoro-pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*,4*R*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-aminocarbonyl-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 3-aminocarbonyl-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 20 a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-carboxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 3-carboxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 25 a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-(*N,N*-diethylaminocarbonyl)phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 3-(*N,N*-diethylaminocarbonyl)phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 30 a compound wherein  $R_1$  is phenyl, Y is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)

- a compound wherein R<sub>1</sub> is naphthalen-2-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is naphthalen-1-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 5 a compound wherein R<sub>1</sub> is pyridin-4-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is furan-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 10 a compound wherein R<sub>1</sub> is thiophen-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is pyrimidin-5-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 15 a compound wherein R<sub>1</sub> is 5-fluoro-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 5-cyano-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-hydroxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 20 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazin-1-yl;
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form 4-methyl-piperazin-1-yl;
- 25 a compound wherein R<sub>1</sub> is 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- 30 a compound wherein R<sub>1</sub> is 5-fluoro-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)

- a compound wherein R<sub>1</sub> is pyrimidin-5-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- a compound wherein R<sub>1</sub> is 5-cyano-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- 5 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-3-yl, and R<sub>a</sub> is H; racemic;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 3-hydroxy-2(*R*)-amino-propyl, and R<sub>a</sub> is H;
- 10 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-4-yl, and R<sub>a</sub> is H;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 8-azabicyclo[3.2.1]octan-3-yl, and R<sub>a</sub> is H; mixture of endo / exo
- 15 isomers;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is azetidin-3-yl-methyl, and R<sub>a</sub> is H;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is azetidin-3-yl-methyl, and R<sub>a</sub> is azetidin-3-yl-methyl;
- 20 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 1-azabicyclo[2.2.2]octan-3-yl, and R<sub>a</sub> is H; mixture of endo / exo isomers;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-3-ylmethyl, and R<sub>a</sub> is H; racemic;
- 25 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 3-amino-cyclohexyl, and R<sub>a</sub> is H; mixture of 4 isomers;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 2-(*N*-methylamino)ethyl, and R<sub>a</sub> is H; and
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 2-(*N*-methylamino)ethyl, and R<sub>a</sub> is 2-(*N*-methylamino)ethyl;
- 30 and pharmaceutically acceptable salts thereof.

According to a sixth aspect of the present invention there is provided a pharmaceutical composition comprising a compound as defined according to the first aspect of the present invention and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable  
5 diluent.

According to a seventh aspect of the present invention there is provided a method for treating mild to severe pain in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a  
10 compound as defined according to the first aspect of the present invention.

According to an eighth aspect of the present invention there is provided a method for treating or preventing a disease or condition selected from the group consisting of depression, Parkinson's disease, drug abuse, alcohol abuse, gastritis,  
15 urinary incontinence, premature ejaculation, diarrhea, cardiovascular disease, and respiratory diseases, said method comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, or salt as defined according to the first aspect of the present invention.

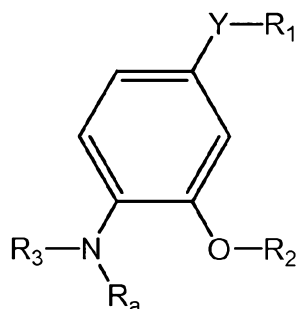
20 According to a ninth aspect of the present invention there is provided use of a compound as defined according to the first aspect of the present invention in the manufacture of a medicament for treating mild to severe pain in a subject.

According to a tenth aspect of the present invention there is provided use of a  
25 compound, or salt as defined according to the first aspect of the present invention in the manufacture of a medicament for treating or preventing a disease or condition selected from the group consisting of depression, Parkinson's disease, drug abuse, alcohol abuse, gastritis, urinary incontinence, premature ejaculation, diarrhea, cardiovascular disease, and respiratory diseases, in a mammal.

30 The present invention is directed to a compound of Formula I

**- END OF PAGE -**





Formula I

wherein

R<sub>1</sub> is selected from the group consisting of

- 5            i)        phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, hydroxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, chloro, and fluoro; such that only one di(C<sub>1-4</sub>alkyl)aminocarbonyl is present;
- ii)        naphthyl;
- 10           iii)        pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, hydroxy, fluoro, chloro, and cyano;
- iv)        pyrimidin-5-yl;
- v)        furanyl;
- 15           vi)        thienyl;
- vii)       5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl; and
- viii)      di(C<sub>1-2</sub>alkyl)aminocarbonyl;

with the proviso that when R<sub>1</sub> is 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, Y is a bond;

Y is ethyl, vinyl, or a bond;

or, Y is O when R<sub>1</sub> is an optionally substituted phenyl;

R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoro, chloro, cyano, trifluoromethoxy, and hydroxy;

or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl, di(C<sub>1-4</sub>alkyl)aminocarbonyl, C<sub>1-4</sub>alkoxycarbonyl, or carboxy substituent;

R<sub>3</sub> is selected from the group consisting of

- i) 3-amino-cyclohexyl;
- ii) 4-amino-cyclohexyl;
- iii) piperidin-3-yl;
- iv) piperidin-4-yl;
- v) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one to two fluoro substituents;
- vi) azetidin-3-ylmethyl;
- vii) 2-(N-methylamino)ethyl;
- viii) 3-hydroxy-2-amino-propyl;
- ix) piperidin-3-ylmethyl;
- x) 1-azabicyclo[2.2.2]octan-3-yl; and
- xi) 8-azabicyclo[3.2.1]octan-3-yl;

or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl optionally substituted with 4-C<sub>1-4</sub>alkyl;

5 R<sub>a</sub> is hydrogen, 2-(N-methylamino)ethyl, or C<sub>1-2</sub>alkyl optionally substituted with azetidin-3-yl;

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

10 The present invention is also directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Formula (I) or a pharmaceutically acceptable salt form thereof.

Also provided are processes for making a pharmaceutical composition comprising mixing a compound of Formula (I) and a pharmaceutically acceptable carrier.  
15

The present invention is further directed to methods for treating or ameliorating an opioid receptor-modulated disorder. In particular, the methods of the present invention are directed to treating or ameliorating an opioid receptor-modulated disorder including, but not limited to, inflammatory pain, centrally mediated pain, peripherally mediated pain, visceral pain, structural related pain, cancer/pain, soft tissue injury related pain,  
20 progressive disease related pain, neuropathic pain and acute pain from acute injury, acute pain from trauma, acute pain from surgery, chronic pain from headache, chronic pain from neuropathic conditions, chronic pain from post-stroke conditions and chronic pain from migraine.

25 The present invention also provides methods for producing the instant compounds and pharmaceutical compositions and medicaments thereof.

As used herein, the following terms are intended to have the following meanings:

“C<sub>a-b</sub>” (where *a* and *b* are integers) refers to a radical containing from *a* to *b* carbon atoms inclusive. For example, C<sub>1-3</sub> denotes a radical containing 1, 2 or 3 carbon atoms.

With reference to substituents, the term “independently” means that when more than one of such substituent is possible, such substituents may be the same or different from each other. Therefore, designated numbers of carbon atoms (e.g. C<sub>1-8</sub>) 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<sub>1-6</sub>alkyl)<sub>2</sub>amino- the C<sub>1-6</sub>alkyl groups of the dialkylamino may be the same or different.

“Halogenated alkyl” refers to a saturated branched or straight chain alkyl radical derived by removal of 1 hydrogen atom from the parent alkane; the parent alkyl chain contains from 1 to 8 carbon atoms with 1 or more hydrogen atoms replaced with halogen atoms up to and including replacement of all hydrogen atoms with halogen. Preferred halogenated alkyl groups include trifluoromethyl substituted alkyls, difluoromethyl substituted alkyls, and perfluorinated alkyls; more preferred fluorinated alkyls include trifluoromethyl and difluoromethyl.

25

“Halogenated alkoxy” refers to a radical derived from a halogenated alkyl, radical attached to an oxygen atom with the oxygen atom having one open valence for attachment to a parent structure.

The term "cycloalkyl" refers to saturated or partially unsaturated, monocyclic or polycyclic hydrocarbon of from 3 to 20 carbon atom members (preferably from 3 to 14 carbon atom members). Examples of such groups include, and are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or adamantyl. The term  
5 cycloalkyl includes a cycloalkyl ring fused to a benzene ring (benzo fused cycloalkyl), or 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 monocyclic ring of 5 to 10 members  
10 in which 1 to 4 members are nitrogen or a nonaromatic monocyclic ring of 5 to 10 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, one or two unsaturated bonds. The term heterocyclyl includes a heterocyclyl 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  
15 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  
20 partially saturated heterocyclyl ring. Additionally, heterocyclyl includes a heterocyclic ring bridged to form bicyclic rings. Preferred partially saturated heterocyclyl rings may have from one to two double bonds. 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,  
25 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.  
30 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. The term heteroaryl includes a heteroaryl ring fused to a benzene ring (benzofused heteroaryl), a 5 or 6 membered heteroaryl ring (containing one of O, S or N and, optionally, one additional nitrogen), a 5 to 7 membered cycloalkyl ring or a 5 to 7 membered heterocyclic 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, benzofuryl, benzothienyl, indazolyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, quinoxaliny, 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.

The term "vinyl" refers to a two-carbon unsaturated linker in which the unsaturation is a double bond between said two carbon atoms. When two substituents occur on the vinyl linker, the substituents are understood to be bound on adjacent carbon atoms, such that the

substituents are 1,2- configured.

The term “oxo” whether used alone or as part of a substituent group refers to an O= to either a carbon or a sulfur atom. For example, phthalimide and saccharin are examples of  
5 compounds with oxo substituents.

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.*,  
10 C<sub>1</sub>-C<sub>6</sub>) 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<sub>1-6</sub> alkyl would include methyl, ethyl, propyl,  
15 butyl, pentyl and hexyl individually as well as sub-combinations thereof (*e.g.* C<sub>1-2</sub>, C<sub>1-3</sub>, C<sub>1-4</sub>, C<sub>1-5</sub>, C<sub>2-6</sub>, C<sub>3-6</sub>, C<sub>4-6</sub>, C<sub>5-6</sub>, C<sub>2-5</sub>, etc.).

The term “subject” as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

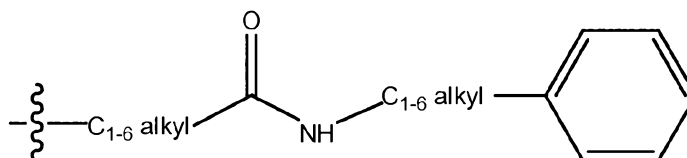
The term “therapeutically effective amount” as used herein, means that amount of  
20 active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which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

As used herein, the term “composition” is intended to encompass a product  
25 comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

As used herein, the term “acyl” refers to alkylcarbonyl substituents.

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 “phenyl(C<sub>1-6</sub>)alkylaminocarbonyl(C<sub>1-6</sub>)alkyl” substituent refers to a group of the formula

5



Unless otherwise noted, 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 formula (I) 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.

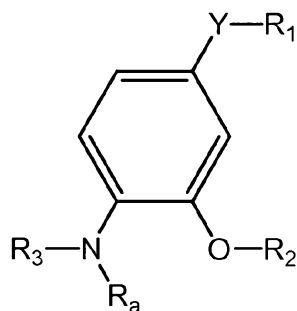
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For purposes of the present invention, the term “opioid receptor-modulated” is used to refer to the condition of being affected by the modulation of an opioid receptor, including but not limited to, the state of being mediated by the opioid receptor.

20

Embodiments of the present invention include those compounds of Formula (I)





Formula (I)

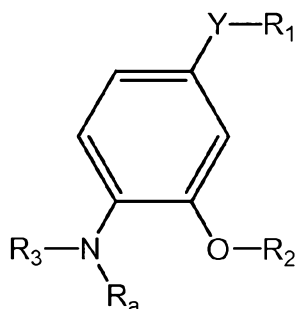
wherein

- a) R<sub>1</sub> is selected from the group consisting of
  - 5      i)      phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, and fluoro; such that only one di(C<sub>1-4</sub>alkyl)aminocarbonyl is present;
  - ii)      naphthyl;
  - 10      iii)     pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
  - iv)      pyrimidin-5-yl;
  - v)      furanyl;
  - vi)      thienyl; and
  - 15      vii)     di(C<sub>1-2</sub>alkyl)aminocarbonyl;
- b) R<sub>1</sub> is selected from the group consisting of
  - i)      phenyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, and fluoro;

- ii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
  - iii) pyrimidin-5-yl; and
  - iv) di(C<sub>1-2</sub>alkyl)aminocarbonyl;
- 5 c) R<sub>1</sub> is selected from the group consisting of
- i) phenyl optionally substituted with one methoxy substituent;
  - ii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
  - iii) pyrimidin-5-yl; and
  - 10 iv) di(C<sub>1-2</sub>alkyl)aminocarbonyl;
- d) Y is vinyl or a bond; or, Y is O when R<sub>1</sub> is an optionally substituted phenyl;
- e) Y is vinyl or a bond;
- f) R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoro, chloro, and  
15 hydroxy;  
or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl or di(C<sub>1-4</sub>alkyl)aminocarbonyl substituent;
- g) R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, and hydroxy;  
20 or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl or di(C<sub>1-4</sub>alkyl)aminocarbonyl substituent;
- h) R<sub>2</sub> is phenyl optionally substituted with one substituent independently selected from the group consisting of methoxy, hydroxy, aminocarbonyl, and di(C<sub>1-4</sub>alkyl)aminocarbonyl;
- 25 i) R<sub>3</sub> is selected from the group consisting of

- i) 3-amino-cyclohexyl;
- ii) 4-amino-cyclohexyl;
- iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one to two fluoro substituents;
- 5 iv) 2-(N-methylamino)ethyl;
- v) piperidin-3-ylmethyl; and
- vi) 1-azabicyclo[2.2.2]octan-3-yl;  
or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl;
- 10 j) R<sub>3</sub> is selected from the group consisting of
  - i) 3-amino-cyclohexyl;
  - ii) 4-amino-cyclohexyl; and
  - iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one fluoro substituent;
- 15 or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl;
- k) R<sub>a</sub> is hydrogen or C<sub>1-2</sub>alkyl;
- l) R<sub>a</sub> is hydrogen;
- and any combination of embodiments a) through l) above, provided that it is
- 20 understood that combinations in which different embodiments of the same substituent would be combined are excluded; and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

A further embodiment of the present invention includes compounds of Formula (I)



Formula (I)

wherein

- 5     R<sub>1</sub> is selected from the group consisting of
  - i)     phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, and fluoro; such that only one di(C<sub>1-4</sub>alkyl)aminocarbonyl is present;
  - 10     ii)    naphthyl;
  - iii)   pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
  - iv)    pyrimidin-5-yl;
  - v)     furanyl;
  - 15     vi)    thienyl; and
  - vii)   di(C<sub>1-2</sub>alkyl)aminocarbonyl;

Y is vinyl or a bond; or, Y is O when R<sub>1</sub> is an optionally substituted phenyl;

- 20     R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoro, chloro, and hydroxy;

or,  $R_2$  is phenyl substituted with one aminocarbonyl or di( $C_{1-4}$ alkyl)aminocarbonyl substituent;

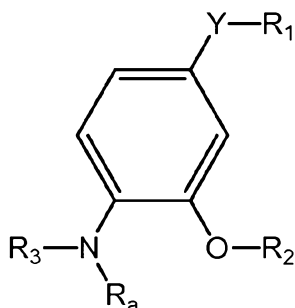
$R_3$  is selected from the group consisting of

- 5            i)        3-amino-cyclohexyl;
  - ii)        4-amino-cyclohexyl;
  - iii)       pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one to two fluoro substituents;
  - v)        2-(N-methylamino)ethyl;
  - 10           vi)        piperidin-3-ylmethyl; and
  - vii)       1-azabicyclo[2.2.2]octan-3-yl;
- or,  $R_3$  is taken with  $R_a$  and the nitrogen atom to which they are both attached to form piperazinyl;

15         $R_a$  is hydrogen or  $C_{1-2}$ alkyl;

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

A further embodiment of the present invention includes compounds of Formula (I)



Formula (I)

wherein

R<sub>1</sub> is selected from the group consisting of

- i) phenyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, and fluoro;
- 5 ii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
- iii) pyrimidin-5-yl; and
- iv) di(C<sub>1-2</sub>alkyl)aminocarbonyl;

10 Y is vinyl or a bond;

R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, and hydroxy;

or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl or di(C<sub>1-4</sub>alkyl)aminocarbonyl  
15 substituent;

R<sub>3</sub> is selected from the group consisting of

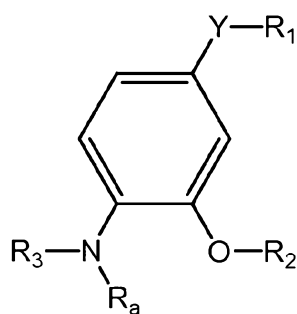
- i) 3-amino-cyclohexyl;
- ii) 4-amino-cyclohexyl;
- 20 iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at a carbon atom with one to two fluoro substituents;
- v) 2-(N-methylamino)ethyl;
- vi) piperidin-3-ylmethyl; and
- vii) 1-azabicyclo[2.2.2]octan-3-yl;

or,  $R_3$  is taken with  $R_a$  and the nitrogen atom to which they are both attached to form piperazinyl;

$R_a$  is hydrogen;

5 and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

A further embodiment of the present invention includes compounds of Formula (I)



10

Formula (I)

wherein

$R_1$  is selected from the group consisting of

- i) phenyl optionally substituted with one methoxy substituent;
- ii) pyridinyl optionally substituted with one substituent selected from the group  
15 consisting of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylthio, fluoro, and cyano;
- iii) pyrimidin-5-yl; and
- iv) di( $C_{1-2}$ alkyl)aminocarbonyl;

Y is vinyl or a bond;

20

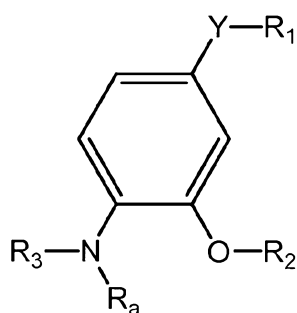
R<sub>2</sub> is phenyl optionally substituted with one substituent independently selected from the group consisting of methoxy, hydroxy, aminocarbonyl, and di(C<sub>1-4</sub>alkyl)aminocarbonyl;

- 5 R<sub>3</sub> is selected from the group consisting of
- i) 3-amino-cyclohexyl;
  - ii) 4-amino-cyclohexyl;
  - iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at a carbon atom with one fluoro substituent;
- 10 or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl;

R<sub>a</sub> is hydrogen;  
and enantiomers, diastereomers, solvates, and pharmaceutically acceptable salts thereof.

15

A further embodiment of the present invention includes compounds of Formula (I)



Formula (I)

- 20 selected from the group consisting of



- a compound wherein R<sub>1</sub> is 2-(*N,N*-diethylaminocarbonyl), Y is (*E*)-vinyl, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 2-(*N,N*-diethylaminocarbonyl), Y is ethyl, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 5 a compound wherein R<sub>1</sub> is 2-(4-methoxy-phenyl), Y is ethyl, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 2-(3-methoxy-phenyl), Y is ethyl, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 2-phenyl, Y is ethyl, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 10 a compound wherein R<sub>1</sub> is 2-(4-fluoro-phenyl), Y is ethyl, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 2-(3-fluoro-phenyl), Y is ethyl, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 15 a compound wherein R<sub>1</sub> is 2-[3-(*N,N*-diethylaminocarbonyl)phenyl], Y is ethyl, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is *N,N*-diethylaminocarbonyl, Y is a bond, R<sub>2</sub> is phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is *N,N*-diethylaminocarbonyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 20 a compound wherein R<sub>1</sub> is *N,N*-diethylaminocarbonyl, Y is a bond, R<sub>2</sub> is 2-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-cyano-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)

- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-cyano-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 5 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-fluoro-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-trifluoromethoxy-phenyl, R<sub>3</sub> is  
10 pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 2,6-dichloro-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 2-(*N*-methylamino)ethyl, and R<sub>a</sub> is H;
- 15 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxycarbonyl-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-methoxycarbonyl-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 2,4-dichloro-phenyl, R<sub>3</sub> is pyrrolidin-  
20 2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-4-yl, and R<sub>a</sub> is H;
- a compound wherein R<sub>1</sub> is 5-cyano-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)

- a compound wherein R<sub>1</sub> is 5-fluoro-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)
- a compound wherein R<sub>1</sub> is 5-methylthio-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)
- 5 a compound wherein R<sub>1</sub> is 5-methoxy-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)
- a compound wherein R<sub>1</sub> is 5-methyl-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)
- 10 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-aminocarbonyl-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-aminocarbonyl-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-carboxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 15 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-carboxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-(N,N-diethylaminocarbonyl)phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-(N,N-diethylaminocarbonyl)phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 20 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is naphthalen-2-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)

- a compound wherein R<sub>1</sub> is naphthalen-1-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is pyridin-4-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 5 a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is furan-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is thiophen-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 10 a compound wherein R<sub>1</sub> is pyrimidin-5-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 5-fluoro-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 15 a compound wherein R<sub>1</sub> is 5-cyano-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-hydroxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazin-1-yl;
- 20 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form 4-methyl-piperazin-1-yl;
- a compound wherein R<sub>1</sub> is 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 25

- a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- a compound wherein R<sub>1</sub> is 5-fluoro-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- 5 a compound wherein R<sub>1</sub> is pyrimidin-5-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- a compound wherein R<sub>1</sub> is 5-cyano-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- 10 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-3-yl, and R<sub>a</sub> is H; racemic
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 3-hydroxy-2(*R*)-amino-propyl, and R<sub>a</sub> is H;
- 15 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-4-yl, and R<sub>a</sub> is H;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 8-azabicyclo[3.2.1]octan-3-yl, and R<sub>a</sub> is H; mixture of endo / exo isomers
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is azetidin-3-yl-methyl, and R<sub>a</sub> is H;
- 20 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is azetidin-3-yl-methyl, and R<sub>a</sub> is azetidin-3-yl-methyl;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 1-azabicyclo[2.2.2]octan-3-yl, and R<sub>a</sub> is H; mixture of endo / exo isomers

a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-3-ylmethyl, and R<sub>a</sub> is H; racemic

a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 3-amino-cyclohexyl, and R<sub>a</sub> is H; mixture of 4 isomers

5 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 2-(N-methylamino)ethyl, and R<sub>a</sub> is H; and

a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 2-(N-methylamino)ethyl, and R<sub>a</sub> is 2-(N-methylamino)ethyl;

and pharmaceutically acceptable salts thereof.

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For use in medicine, salts of compounds of formula (I) refer to non-toxic “pharmaceutically acceptable salts.” Other salts may, however, be useful in the preparation of compounds of formula (I) or of their pharmaceutically acceptable salts thereof. Suitable pharmaceutically acceptable salts of compounds of formula (I) include  
15 acid addition salts which can, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid.

Furthermore, where the compounds of formula (I) carry an acidic moiety, suitable  
20 pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium  
25 edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate,

methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teclate, tosylate, triethiodide and valerate.

5

Representative acids and bases which may be used in the preparation of pharmaceutically acceptable salts include the following: acids including acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid,  $\alpha$ -oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, ( $\pm$ )-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, ( $\pm$ )-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebaic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid;

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15  
20

and bases including ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

25

Embodiments of the present invention include prodrugs of compounds of formula (I). In general, such prodrugs will be functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment

30

of embodiments of the present invention, the term “administering” encompasses 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 a patient. 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 embodiments of 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. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention. 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. The skilled artisan will understand that the term compound as used herein, is meant to include solvated compounds of Formula I.

Where the processes for the preparation of the compounds according to certain embodiments of the invention give rise to a mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric 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 diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using a chiral HPLC column.

One embodiment of the present invention is directed to a composition comprising the (+)-enantiomer of a compound of formula (I) wherein said composition is



substantially free from the (-)-isomer of said compound. In the present context, substantially free means less than 25 %, preferably less than 10 %, more preferably less than 5 %, even more preferably less than 2 % and even more preferably less than 1 % of the (-)- isomer calculated as.

5

$$\% (+) - \text{enantiomer} = \frac{(\text{mass} (+) - \text{enantiomer})}{(\text{mass} (+) - \text{enantiomer}) + (\text{mass} (-) - \text{enantiomer})} \times 100$$

Another embodiment of the present invention is a composition comprising the (-)-enantiomer of a compound of formula (I) wherein said composition is substantially free  
 10 from the (+)-isomer of said compound. In the present context, substantially free from means less than 25 %, preferably less than 10 %, more preferably less than 5 %, even more preferably less than 2 % and even more preferably less than 1 % of the (+)- isomer calculated as

$$15 \quad \% (-) - \text{enantiomer} = \frac{(\text{mass} (-) - \text{enantiomer})}{(\text{mass} (+) - \text{enantiomer}) + (\text{mass} (-) - \text{enantiomer})} \times 100 .$$

During any of the processes for preparation of the compounds of embodiments of the present invention, it may be necessary and/or desirable to protect sensitive or reactive  
 20 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 from the art.

25 Even though the compounds of embodiments of the present invention (including their pharmaceutically acceptable salts and pharmaceutically acceptable solvates) can be administered alone, they will generally be administered in admixture with a pharmaceutical carrier, excipient or diluent selected with regard to the intended route of administration and

standard pharmaceutical practice. Thus, particular embodiments of the present invention are directed to pharmaceutical compositions comprising compounds of formula (I) and one or more than one pharmaceutically acceptable carrier, excipient or diluent.

By way of example, in the pharmaceutical and veterinary compositions of  
5   embodiments of the present invention, the compounds of formula (I) may be admixed with any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), and/or solubilizing agent(s).

Tablets or capsules of the compounds may be administered one or two or more at a time, as appropriate. It is also possible to administer the compounds in sustained release  
10   formulations.

Alternatively, compounds of formula (I) can be administered by inhalation (intratracheal or intranasal) or in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion of  
15   polyethylene glycols or liquid paraffin. They can also be incorporated, at a concentration of between 1 % and 10 % by weight, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required. An alternative means of transdermal administration is by use of a skin patch.

For some applications, preferably the compositions are administered orally in the  
20   form of tablets containing excipients such as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavoring or coloring agents.

The compositions (as well as the compounds alone) can also be injected parenterally, for example intracavernosally, intravenously, intramuscularly,  
25   subcutaneously, intradermally or intrathecally. In this case, the compositions will comprise a suitable carrier or diluent.

For parenteral administration, the compositions are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or monosaccharides to make the solution isotonic with blood.

For buccal or sublingual administration, the compositions may be administered in the form of tablets or lozenges, which can be formulated in a conventional manner.

By way of further example, pharmaceutical and veterinary compositions containing one or more of the compounds of formula (I) as the active ingredient can be prepared by intimately mixing the compound or compounds with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending upon the desired route of administration (e.g., oral, parenteral, etc.). Thus for liquid oral preparations such as suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, stabilizers, coloring agents and the like; for solid oral preparations, such as powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Solid oral preparations also may be coated with substances such as sugars or be enterically -coated so as to modulate the major site of absorption. For parenteral administration, the carrier will usually consist of sterile water, and other ingredients may be added to increase solubility or preservation. Injectable suspensions or solutions may also be prepared utilizing aqueous carriers along with appropriate additives.

A therapeutically effective amount of compounds of formula (I) or a pharmaceutical composition thereof comprises a dose range from about 0.1 mg to about 3000 mg, in particular from about 1 mg to about 1000 mg or, more particularly, from about 10 mg to about 500 mg of active ingredient in a regimen of about 1 to 4 times per day for an average (70 kg) human; although, it is apparent to one skilled in the art that the therapeutically effective amount for active compounds of the invention will vary as will the conditions being treated.

For oral administration, a pharmaceutical composition is preferably provided in the form of tablets containing 0.01, 10.0, 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.

Advantageously, compounds of formula (I) 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. Furthermore, compounds of formula (I) can be administered in intranasal

form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those skilled in that art.

It is also apparent to one skilled in the art that the therapeutically effective dose for active compounds of formula (I) or a pharmaceutical composition thereof will vary according to the desired effect. Therefore, optimal dosages to be administered may be readily determined 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 achieve an appropriate therapeutic level. The above dosages are thus exemplary of the average case. There can be, of course, individual instances wherein higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of formula (I) 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 use of the compounds of formula (I) as analgesics is required for a subject in need thereof.

Examples of pain intended to be within the scope of the present invention include, but are not limited to, inflammatory pain, centrally mediated pain, peripherally mediated pain, visceral pain, structural or soft tissue injury related pain, progressive disease related pain, neuropathic pain and acute pain such as caused by acute injury, trauma or surgery and chronic pain such as headache and that caused by neuropathic conditions, post-stroke conditions, cancer, and migraine.

Compounds of the present invention are also useful as immunosuppressants, antiinflammatory agents, agents for the treatment and prevention of neurological and psychiatric conditions, for instance, depression and Parkinson's disease, agents for the treatment of urological and reproductive conditions, for instance, urinary incontinence and premature ejaculation, medicaments for drug and alcohol abuse, agents for treating gastritis

and diarrhea, cardiovascular agents and cardioprotective agents and agents for the treatment of respiratory diseases.

The compounds of the present invention are also useful in treating pain caused by

5 osteoarthritis, rheumatoid arthritis, fibromyalgia, migraine, headache, toothache, burn, sunburn, snake bite (in particular, venomous snake bite), spider bite, insect sting, neurogenic bladder, benign prostatic hypertrophy, interstitial cystitis, rhinitis, contact dermatitis/hypersensitivity, itch, eczema, pharyngitis, mucositis, enteritis, cellulitis, causalgia, sciatic neuritis, mandibular joint neuralgia, peripheral neuritis, polyneuritis,

10 stump pain, phantom limb pain, post-operative ileus, cholecystitis, postmastectomy pain syndrome, oral neuropathic pain, Charcot's pain, reflex sympathetic dystrophy, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, optic neuritis, postfebrile neuritis, migrating neuritis, segmental

15 neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, migrainous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia, vidian neuralgia, inflammatory bowel disease, irritable bowel

20 syndrome, sinus headache, tension headache, labor, childbirth, menstrual cramps, and cancer.

In regard to the use of the present compounds in treatment of the diseases or conditions such as those listed above, a therapeutically effective dose can be determined by

25 persons skilled in the art by the use of established animal models. The therapeutically effective dose of the compounds of Formula (I) exemplified in such a treatment is from about 0.001 mg/kg/day to about 300 mg/kg/day. Particularly, the range is from about 0.5 to about 5.0 mg/kg of body weight per day; and more particularly, from about 1.0 to about 3.0

mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

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## GENERAL SYNTHETIC METHODS

Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described below and illustrated in the schemes and examples that follow. Since the schemes are an illustration, the invention should not be construed as being limited by the chemical reactions and conditions described in the schemes. The various starting materials used in the schemes and examples are commercially available or may be prepared by methods well within the skill of persons versed in the art. The variables are as defined herein.

Abbreviations used in the instant specification, particularly the schemes and examples, are as follows:

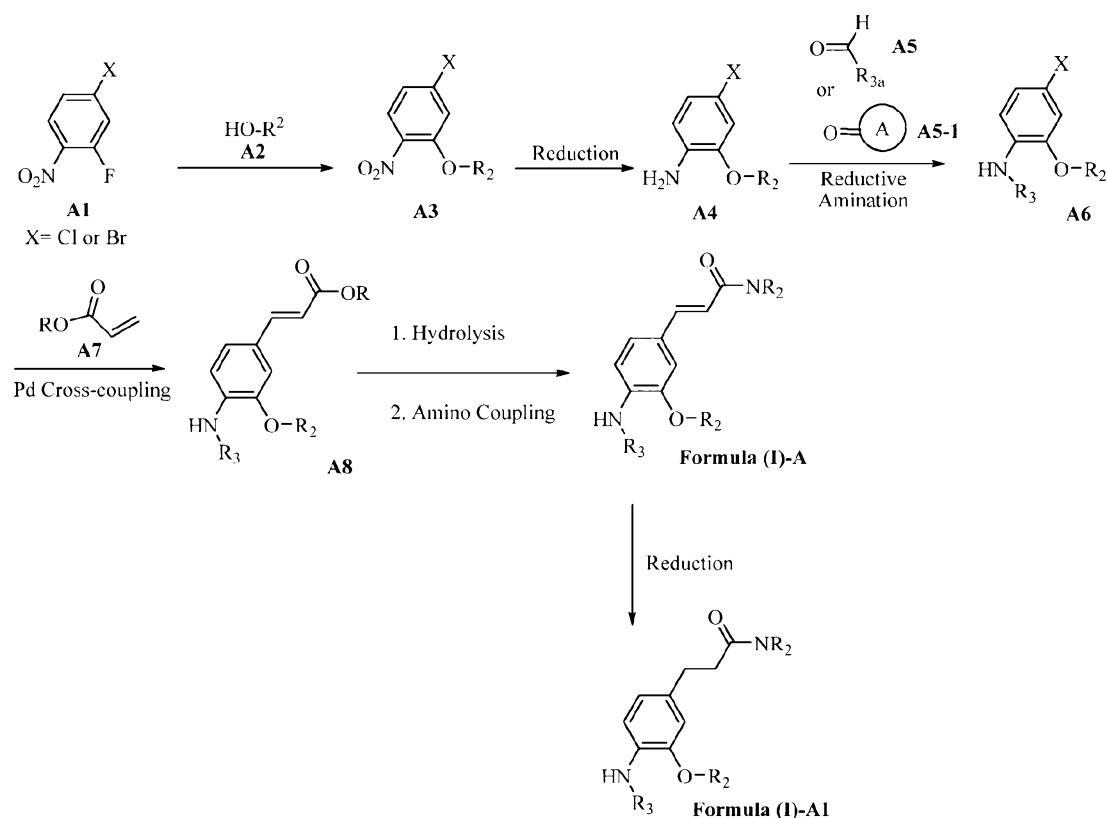
	AcCl	acetyl chloride
	AcOH	glacial acetic acid
	aq.	aqueous
	Bn or Bzl	benzyl
20	CDI	N,N'-carbonyldiimidazole
	conc.	concentrated
	DAMGO	Tyr-D-Ala-Gly-(methyl)Phe-Gly-ol
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
	DCE	1,2-dichloroethane
25	DCM	dichloromethane
	DIEA	diisopropylethylamine
	DMF	N,N-dimethylformamide
	DMSO	dimethylsulfoxide
	DPDPE	[D-Pen2,D-Pen5]-enkephalin

	dppf	1,1'-bis(diphenylphosphino)ferrocene
	EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
	ESI	electron-spray ionization
	EtOAc	ethyl acetate
5	EtOH	ethanol
	h or hrs	hour(s)
	HATU	<i>O</i> -(1 <i>H</i> -7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl-uronium-hexafluorophosphate
10	HBTU	<i>O</i> -(1 <i>H</i> -benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
	HEPES	2-[4-(2-hydroxyethyl)-1-piperazinyl] ethanesulfonic acid
	HOBt	N-hydroxybenzotriazole
	HPLC	high performance liquid chromatography
15	Me	methyl
	MeOH	methanol
	MHz	megahertz
	min	minutes
	MPLC	medium pressure liquid chromatography
20	MS	mass spectrometry
	NMR	nuclear magnetic resonance
	NT	not tested
	Ph	phenyl
	Pd/C	palladium on activated carbon
25	Ph <sub>3</sub> P	triphenylphosphine
	PPA	polyphosphoric acid
	PyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
	rt	room temperature
30	TBDMS	<i>tert</i> -butyldimethylsilyl

	TEA/ Et <sub>3</sub> N	triethylamine
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin layer chromatography
5	TMS	tetramethylsilane or trimethylsilyl

Scheme A illustrates the preparation of compounds of Formula (I)-A and Formula (I)-A1 wherein Y is vinyl or ethyl, respectively, R<sub>1</sub> is di(C<sub>1-2</sub>alkyl)aminocarbonyl, and R<sub>3</sub> is as defined herein. R<sub>3a</sub> of compound **A5** is defined as (N-methylamino)methyl, pyrrolidin-2-yl, azetidin-3-yl, or piperidin-3-yl. Ring A of compound **A5-1** is defined as 3- or 4-amino-cyclohexyl, piperidin-3-yl, piperidin-4-yl,

#### Scheme A



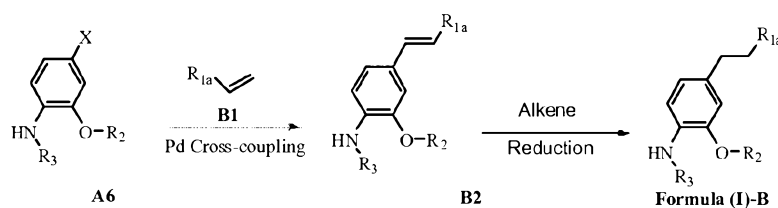
Compound **A1** is either commercially available or can be made by known methods described in the scientific literature. Reaction with an appropriately substituted alcohol of



formula **A2**, optionally in the presence of a base, affords a compound of formula **A3**. The nitro group of a compound of formula **A3** may be reduced to the corresponding amino group by the action of a reducing agent such as zinc metal in the presence of acetic acid in an organic solvent such as methanol, or by the action of sodium borohydride in the presence of nickel chloride or a catalytic hydrogenation. The resultant aniline of formula **A4** may be alkylated with an  $R_{3a}$ -substituted aldehyde (**A5**) or a ketone of formula **A5-1**, in the presence of a reducing agent such as sodium triacetoxyborohydride in acetic acid to afford a compound of formula **A6**. A palladium catalyzed coupling with a compound of formula **A7**, wherein R is  $C_{1-4}$ alkyl, in the presence or absence of added ligands for palladium such as dppf or tri-*o*-tolylphosphine, affords an alkene of formula **A8**. The alkoxy carbonyl group of a compound of formula **A8** may be saponified in the presence of hydroxide ion to form its corresponding carboxylic acid, which may then be coupled with a di( $C_{1-4}$  alkyl)amine, in the presence of an appropriate coupling agent such as EDCI, and an activating agent such as HOBt, to form an amide of formula (I)-A. Reduction of the alkenyl group of a compound of formula (I)-A with a reducing agent such as catalytic hydrogenation affords a compound of formula (I)-A1. One skilled in the art will recognize that certain compounds of formula **A5** and **A5-1** may require an amino protecting group (P), which may be carried through subsequent chemical steps of the synthetic scheme. Conventional chemical methods may be used for amino deprotection at a later stage. For example, a Boc group may be removed by the action of a mineral acid or by an organic acid such as trifluoroacetic acid.

Scheme B illustrates the preparation of compounds of Formula (I)-B wherein Y is ethyl, and  $R_{1a}$  is optionally substituted phenyl, naphthyl, optionally substituted pyridinyl, pyrimidin-5-yl, furanyl, or thienyl.

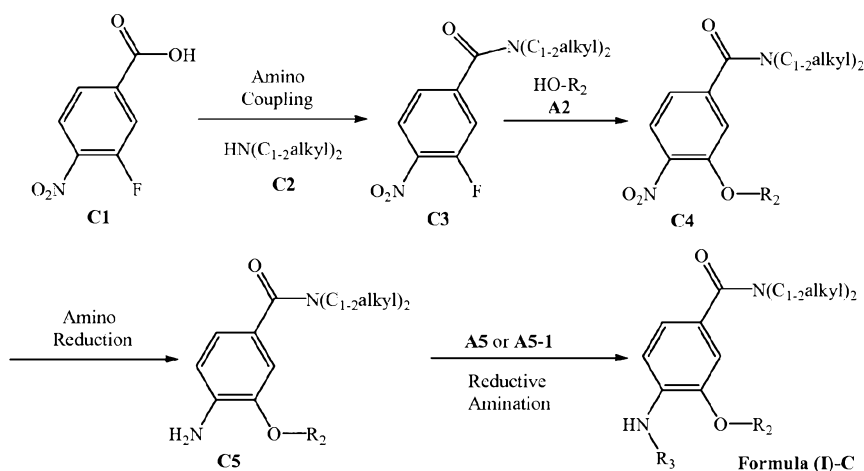
#### Scheme B



A compound of formula **A6** may be coupled with a compound of formula **B1** wherein  $R_{1a}$  is defined herein, in the presence of a palladium catalyst and in the presence or absence of added ligands for palladium, and in the presence of an organic base such as TEA to afford an alkene of formula **B2**. Reduction of the alkenyl functionality may be achieved by a transition metal-catalyzed hydrogenation to afford, upon optional amino deprotection, a compound of formula **(I)-B**.

Scheme C illustrates the preparation of compounds of Formula (I)-C wherein Y is a bond and  $R_1$  is di( $C_{1-2}$ alkyl)aminocarbonyl.

10 Scheme C

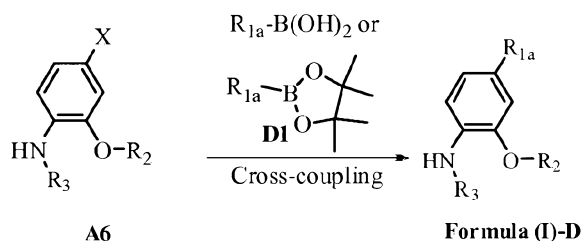


The compound **C1** is either commercially available or can be made by known methods described in the scientific literature. The compound **C1** may be coupled with an amine of formula **C2** in the presence of an appropriate coupling agent such as EDCI, and an activating agent such as HOBt, to afford an amide of formula **C3**. Aromatic nucleophilic substitution with a compound of formula **A2** in the presence of a base affords a compound of formula **C4**. The nitro group of a compound of formula **C4** may be reduced to the corresponding amino group by the action of a reducing agent such as zinc metal in the presence of acetic acid in an organic solvent such as methanol, or by the action of sodium borohydride in the presence of nickel chloride, or a catalytic hydrogenation. The resultant aniline of formula **C5** may be alkylated with an  $R_{3a}$ -substituted aldehyde (**A5**) or ketone of

formula **A5-1**, in the presence of a reducing agent such as sodium triacetoxyborohydride in acetic acid to afford, upon optional amino deprotection, a compound of formula (I)-C.

Scheme D illustrates the preparation of compounds of Formula (I)-D wherein Y is a bond and R<sub>1</sub> is optionally substituted phenyl, naphthyl, optionally substituted pyridinyl, pyrimidin-5-yl, furanyl, or thienyl (represented as R<sub>1a</sub>).

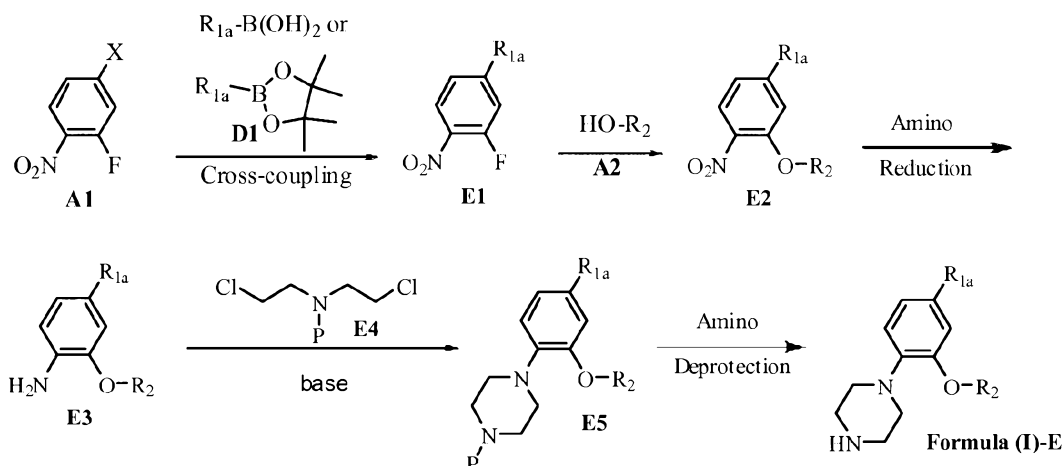
#### Scheme D



The R<sub>1a</sub> group may be introduced into a compound of formula **A6** through a palladium catalyzed cross-coupling reaction with an appropriately substituted boronic acid or boronate ester (**D1**), in the presence of a suitable base such as potassium carbonate. The reaction also may be carried out in the presence or absence of added ligands for palladium which, when used, include one or more than one of triphenylphosphine, tri-O-tolylphosphine, tri(tert-butyl)phosphine, 1,1'-bis(diphenylphosphino)ferrocene, bis[2-(diphenyl-phosphino)phenyl] ether, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, 1-butyl-3-methylimidazolium hexafluorophosphate, and the like. Useful solvents include ethanol, THF, DMF, toluene, DME, dioxane, or benzene. Upon optional amino deprotection, a compound of formula (I)-D may be prepared.

Scheme E illustrates the preparation of compounds of Formula (I)-E wherein Y is a bond, R<sub>1</sub> is optionally substituted phenyl, naphthyl, optionally substituted pyridinyl, pyrimidin-5-yl, furanyl, or thienyl (represented as R<sub>1a</sub>); and R<sub>3</sub> is taken with -N-R<sub>a</sub> to form piperazin-1-yl.

#### Scheme E



The  $R_{1a}$  group may be introduced into a compound of formula **A1** through a palladium catalyzed cross-coupling reaction with an appropriately substituted boronic acid or boronate ester (**D1**), in the presence of a suitable base such as potassium carbonate, as

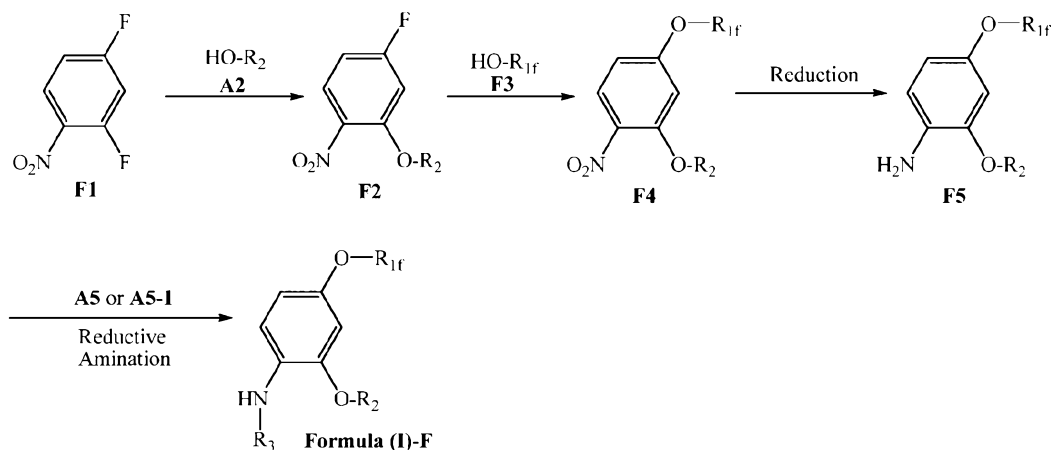
5 further described herein. A compound of formula **E1** may be reacted with a compound of formula **A2** in the presence of a suitable base to form a compound of formula **E2**. The nitro group of a compound of formula **E2** may be reduced to the corresponding aniline as previously described herein to form a compound of formula **E3**. Treatment with a protected amine of formula **E4** in the presence of a suitable base such as potassium carbonate affords

10 a compound of formula **E5**. Removal of amino protecting group (**P**) affords a compound of formula (I)-E.

Scheme F illustrates the preparation of compounds of Formula (I)-F wherein Y is O,  $R_1$  is optionally substituted phenyl (pictured as  $R_{1f}$ ), and  $R_3$  is as defined by the

15 invention.

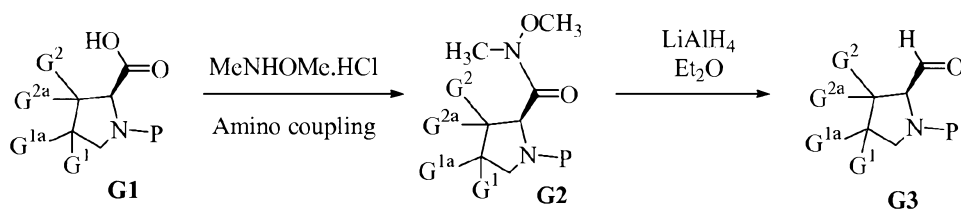
#### Scheme F



A difluoro compound of formula **F1** is either commercially available or readily synthesized according to methods described in the scientific literature. Upon nucleophilic aromatic substitution with a compound of formula **A2**, optionally in the presence of a base, a compound of formula **F2** may be prepared. Subsequent reaction with an  $R_{1f}$ -substituted phenol of formula **F3**, optionally in the presence of a base, affords a compound of formula **F4**. Reduction of the nitro group as previously described affords a compound of formula **F5**. Treatment with an aldehyde of formula **A5** or a ketone of formula **A5-I** in the presence of a hydride source followed by conventional amino deprotection if  $R_3$  contains an amino protecting group provides compounds of formula (I)-F.

Scheme G illustrates the preparation of certain useful  $R_3$  intermediates of the present invention, useful for the synthesis of compounds of Formula (I) wherein  $R_3$  is pyrrolidin-2-yl methyl substituted at the 3- or 4- position with one to two fluoro substituents.

#### Scheme G



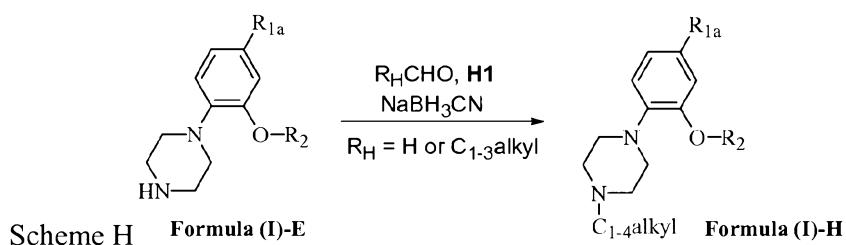
$G^1, G^{1a}, G^2, G^{2a} = \text{H or F}$   
such that no more than two can be F

A compound of formula **G1** is either commercially available or can be prepared according to known methods described in the scientific literature. A compound of formula **G1** (wherein  $G^1$ ,  $G^{1a}$ ,  $G^2$ , and  $G^{2a}$  are each hydrogen or fluoro, such that no more than two of said  $G^1$ ,  $G^{1a}$ ,  $G^2$ , and  $G^{2a}$  can be fluoro) may be treated with *N,O*-dimethylhydroxylamine hydrochloride, in the presence of a peptide coupling agent such as HBTU and an organic base such as DIEA, in an organic solvent such as DMF, to afford a compound of formula **G2**. A compound of formula **G2** may be converted to its corresponding aldehyde of formula **G3** by the action of lithium aluminum hydride. A compound of formula **G3** may be used in an analogous manner to a compound of formula **A5** to form compounds of

10 Formula (I).

Scheme H describes the preparation of compounds of Formula (I)-H wherein  $R_1$  is optionally substituted phenyl, naphthyl, optionally substituted pyridinyl, pyrimidin-5-yl, furanyl, or thienyl (represented as  $R_{1a}$ ); Y is a bond, and  $R_3$  is taken with  $-N-R_a$  to form

15 piperazin-1-yl substituted with 4- $C_{1-4}$ alkyl.

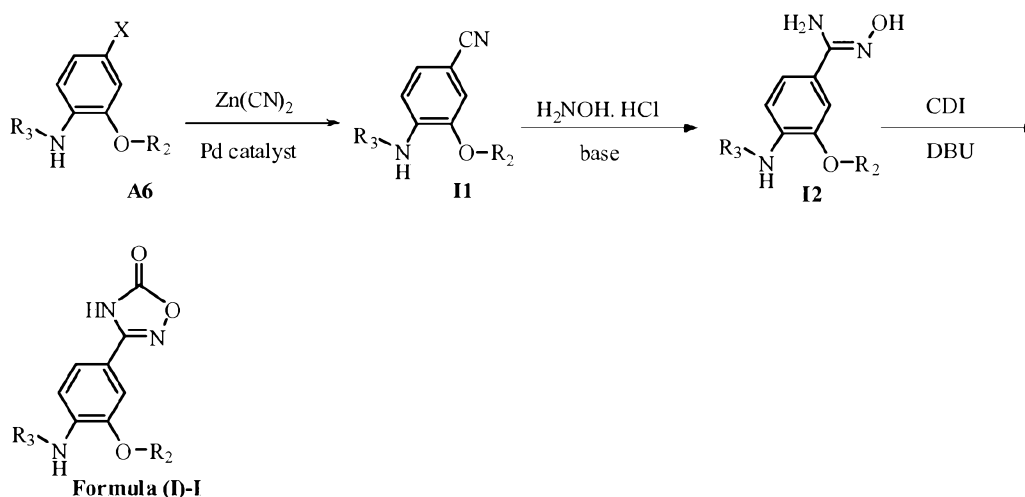


A compound of Formula (I)-E may be reacted with a compound of formula **H1** wherein  $R_H$  is hydrogen or  $C_{1-3}$ alkyl, in the presence of a hydride source such as sodium cyanoborohydride, to form an alkylated product of formula (I)-H.

20

Scheme I illustrates the preparation of compounds of Formula (I)-I wherein Y is a bond,  $R^1$  is 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, and  $R^3$  is as defined herein.

#### Scheme I

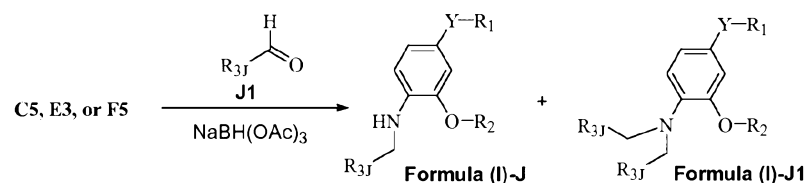


A compound of formula **A6** may be prepared by the synthetic methods described in the schemes provided herein. A compound of formula **A6** may be treated with zinc cyanide in the presence of a palladium catalyst such as  $\text{Pd}(\text{PPh}_3)_4$  to afford a cyanide of formula **II**.

- 5 Reaction of the cyano group with hydroxylamine hydrochloride in the presence of a base affords a compound of formula **I2**. Condensation of a compound of formula **I2** with CDI in the presence of a base such as DBU gives a compound of formula **(I)-I**. Compounds of formula **(I)-I** wherein  $\text{R}_3$  contains an amino protecting group may require conventional removal of the group.

- 10 Scheme J illustrates the preparation of compounds of formula (I)-J and (I)-J1 wherein  $\text{R}_3$  is 2-(N-methylamino)ethyl or azetidin-3-ylmethyl, and  $\text{R}_a$  is hydrogen or 2-(N-methylamino)ethyl, respectively.  $\text{R}_{3J}$  is defined as N-protected methylaminomethyl or N-protected azetidin-3-yl.

#### Scheme J

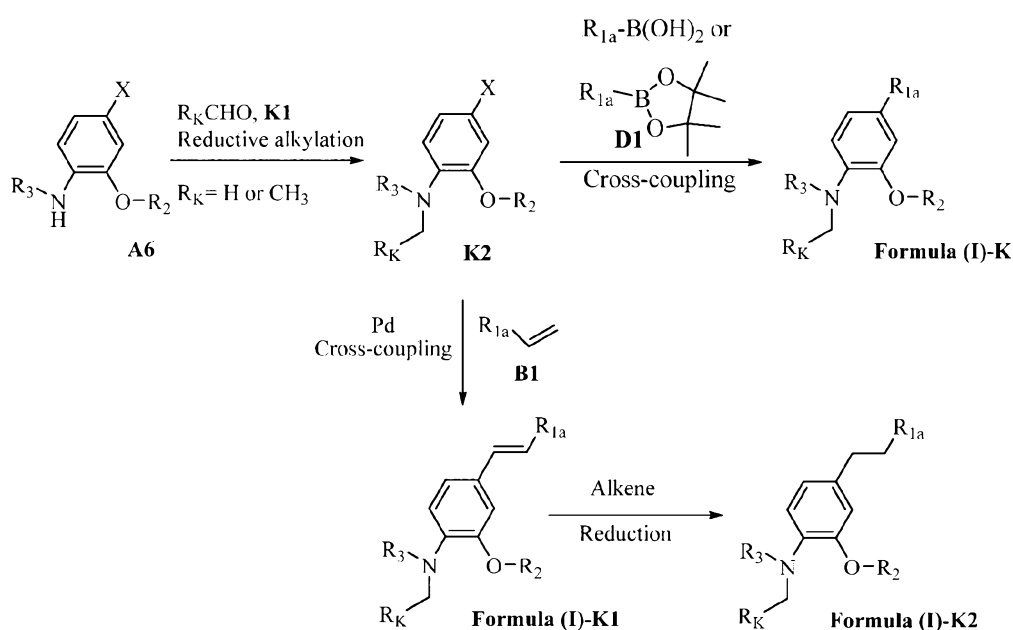


A compound of formula **C5**, **E3**, or **F5** may undergo a reductive alkylation with an aldehyde of formula **J1** in the presence of a hydride source such as sodium triacetoxyborohydride, followed by conventional amino deprotection, to afford a mixture

of compounds of formula (I)-J and formula (I)-J1. Products of formula (I)-J and formula (I)-J1 may be separated using conventional separation methods known to those skilled in the art.

- 5            Scheme K illustrates the preparation of compounds of formula (I)-K, formula (I)-K1, and formula (I)-K2, wherein  $R_1$ , Y, and  $R_3$  are as defined herein and  $R_a$  is optionally substituted  $C_{1-2}$ alkyl as defined herein.

### Scheme K



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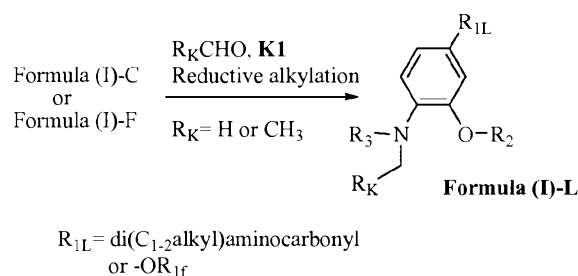
- A compound of formula **A6** may undergo a reductive alkylation with an aldehyde of formula **K1** in the presence of a hydride source such as sodium cyanoborohydride or sodium triacetoxyborohydride to afford a compound of formula **K2**. A compound of formula **K2** may be coupled with a compound of formula **D1** which, upon removal of any chemically necessary protecting groups, may afford, upon optional amino deprotection, a compound of formula (I)-K wherein Y is a bond. Similarly, a compound of formula **K1** may be coupled with a compound of formula **B1** to afford a compound of formula (I)-K1 wherein Y is vinyl. Conventional reduction of the vinyl group as described in Scheme B
- 15



affords, upon optional amino deprotection, a compound of formula (I)-K2 wherein Y is ethyl.

Scheme L illustrates the preparation of compounds of formula (I)-L, wherein  $R_{1L}$  is  
 5 di( $C_{1-2}$ alkyl)aminocarbonyl or  $-OR_{1f}$ ,  $R_3$  is defined herein, and  $R_a$  is optionally substituted  $C_{1-2}$ alkyl as defined herein.

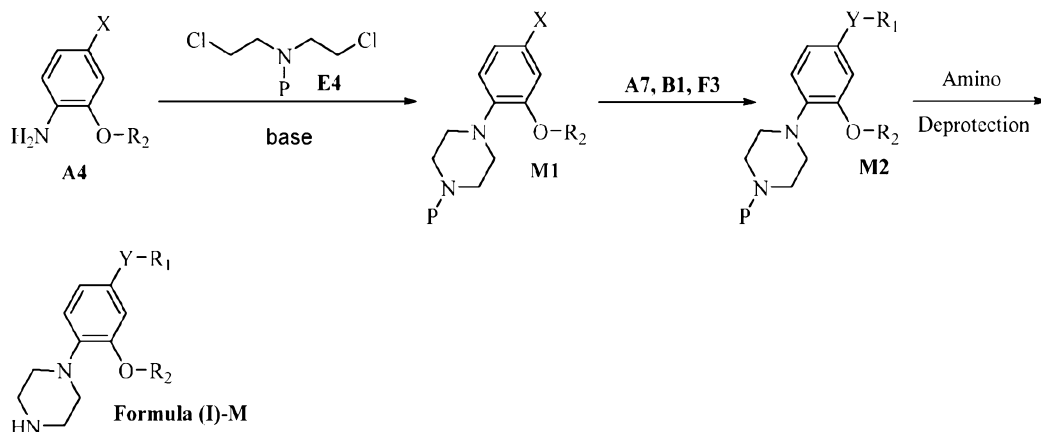
#### Scheme L



A compound of formula (I)-C or formula (I)-F may undergo a reductive alkylation with an  
 10 aldehyde of formula **K1** in the presence of a hydride source such as sodium cyanoborohydride or sodium triacetoxyborohydride to afford, upon optional amino deprotection, a compound of formula (I)-L.

Scheme M illustrates the preparation of compounds of Formula (I)-M wherein Y  
 15 and  $R_1$  are as defined herein, and  $R_3$  is taken with  $-N-R_a$  to form piperazin-1-yl.

#### Scheme M



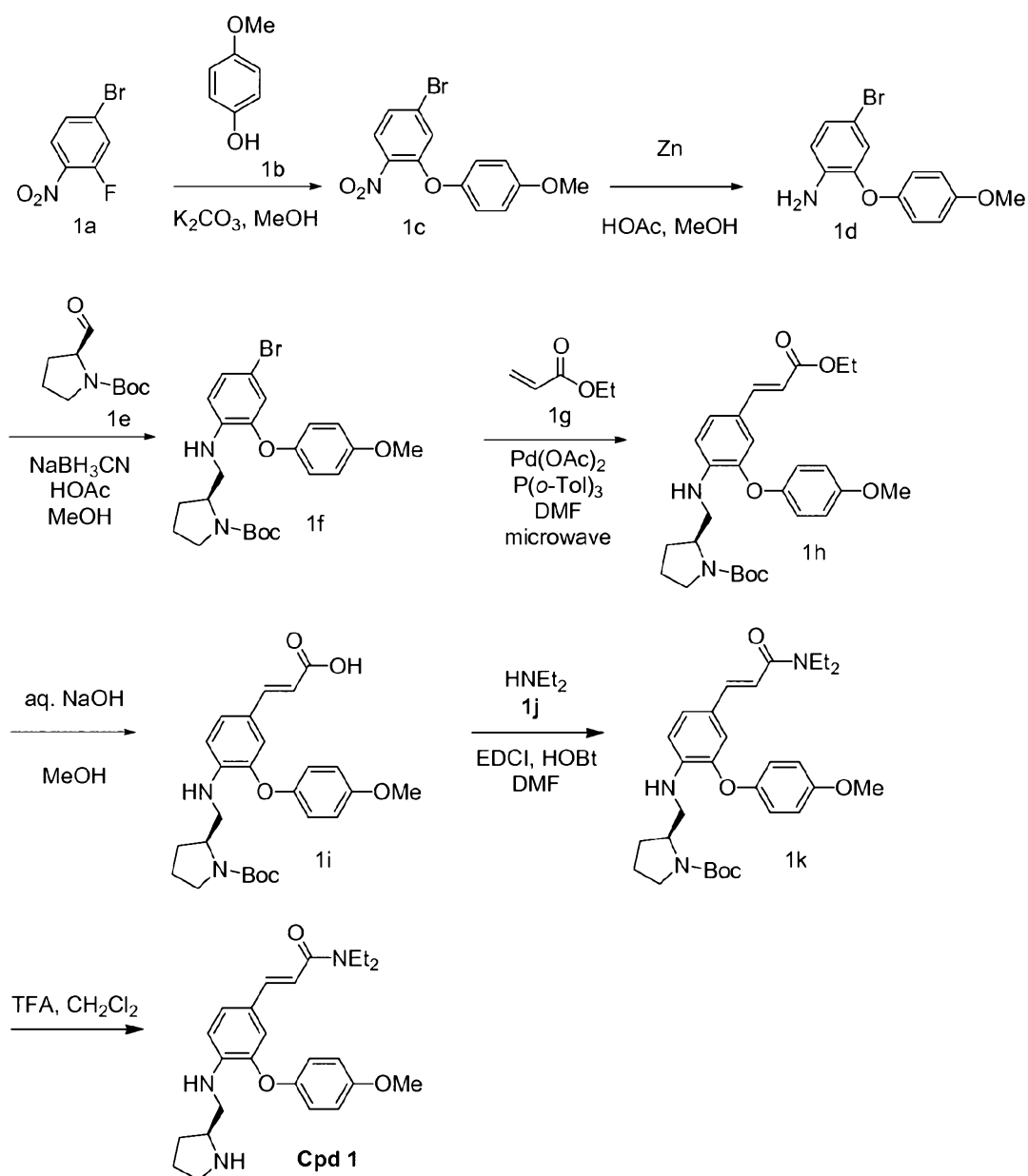
A compound of formula **A4** may be treated with a protected amine of formula **E4** in the presence of a suitable base such as potassium carbonate to afford a compound of formula **M1**. Suitable  $\text{Y}$  and  $\text{R}_1$  groups of the present invention may be installed by reaction with a compound of formula **A7**, **B1**, or **F3**, for example, as taught in the schemes provided herein, to afford a compound of formula **M2**. Amino deprotection using conventional chemistry affords a compound of formula **(I)-M**.

### Specific Examples

Reagents were purchased from commercial sources. Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a Bruker Avance or Varian (300 or 400 MHz) spectrometer. The values are expressed in parts per million downfield from TMS. The mass spectra (MS) were determined on a Micromass Platform LC or Agilent 1100 LCMS spectrometer as (ESI)  $m/z$  ( $\text{M}+\text{H}^+$ ) using an electrospray technique. Microwave accelerated reactions were performed using a CEM Discover or Biotage microwave instrument, and were contained in a sealed pressure vessel unless otherwise noted. 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.

5

**Example 1**

**A. 4-Bromo-2-(4-methoxy-phenoxy)nitrobenzene (1c).** A mixture of Compound **1a** (2.20 g, 10.0 mmol), 4-methoxyphenol (Compound **1b**, 1.32 g, 10.5 mmol), K<sub>2</sub>CO<sub>3</sub> (1.52 g, 11.0 mmol), and 6 mL of DMF was stirred at 75°C for 3 h. The mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc and water. The organic layer was washed successively with 2N aqueous NaOH, 2N aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give Compound **1c** as a brown gel (2.95 g, 91%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.11-7.84 (d, 1H), 7.24-7.27 (m, 1H), 7.01-7.06 (m, 3H), 6.93-6.97 (m, 2H), 3.71 (s, 3H).

**B. 4-Bromo-2-(4-methoxy-phenoxy)-aniline (1d).** A mixture of Compound **1c** (1.64 g, 5.06 mmol), zinc (1.98 g, 30.4 mmol), 15 mL of HOAc, and 50 mL of MeOH was stirred at 20°C for 20 h. After removal of solvents, the residue was partitioned between EtOAc and 3N aqueous NaOH. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give Compound **1d** as a brown oil (1.54 g, 103% yield). MS: *m/z* 294.0 (M + H)<sup>+</sup>.

**C. 2-(S)-{[4-Bromo-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1f).** NaBH<sub>3</sub>CN (0.67 mmol, 10.1 mmol) was added to a mixture of Compound **1d** (1.45 g, 5.06 mmol) and Boc-L-prolinal (Compound **1e**, 1.04 g, 5.06 mmol) in 20 mL of MeOH and 2.5 mL of HOAc. The mixture was stirred at 20°C for 1.5 h. After evaporation of solvent, the residue was extracted with EtOAc. The organic layer was washed successively with 1N aqueous NaOH, 1N aqueous HCl, and brine and was dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration and purification by flash column chromatography (SiO<sub>2</sub>), eluting with a hexanes-ether gradient, afforded Compound **1f** as a yellow oil (2.36 g, 98% yield) MS: *m/z* 476.9, 478.8 (M + H)<sup>+</sup>.

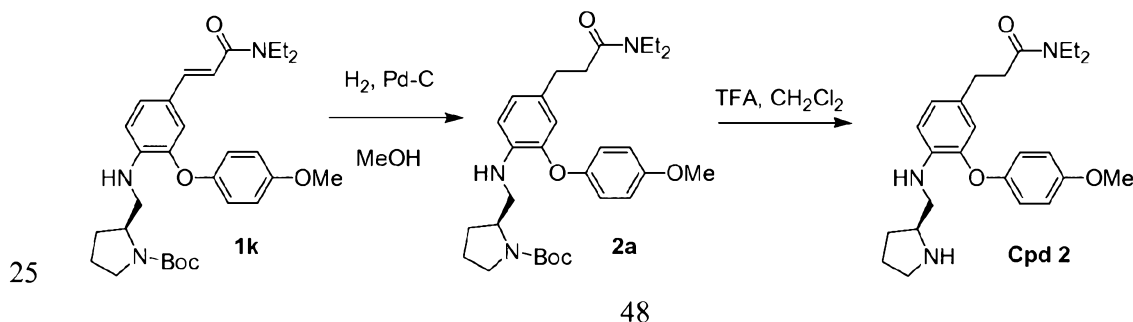
**D. (E)-2-(S)-{[4-(2-Ethoxycarbonyl-ethenyl)-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1h).** A mixture of Compound **1f** (0.19 g, 0.4 mmol), ethyl acrylate (**1g**, 0.43 g, 0.045 mL, 0.5 mmol), Pd(OAc)<sub>2</sub> (0.0009 g, 0.004 mmol), tri-*o*-tolylphosphine (0.0049 g, 0.016 mmol), and 0.4 mL of DMF was irradiated in a microwave reactor for 10 min at 160°C. Purification by preparative TLC, eluting with 3:7 EtOAc:hexanes, gave Compound **1h** as a yellow solid (0.15 g, 78% yield). MS: *m/z* 483.2 (M + H)<sup>+</sup>.

**E. (E)-2-(S)-{[4-(2-Carboxy-ethenyl)-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1i).** A mixture of Compound 1h (0.15 g, 0.31 mmol), 1 mL of 3N aqueous NaOH (3 mmol), and 1 mL of MeOH was stirred at 20°C for 20 h. After evaporation of the MeOH, the aqueous phase was acidified with 1N aqueous HCl and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give Compound 1i (0.18 g, 124% yield). MS: *m/z* 469.3 (M + H)<sup>+</sup>.

**F. 2-(S)-{[4-(2-Diethylcarbamoyl-ethenyl)-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (1k).** A mixture of Compound 1i (0.18 g, 0.38 mmol), N,N-diethylamine (Compound 1j, 0.04 mL, 0.38 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide monohydrochloride (EDC-HCl, 0.095 g, 0.49 mmol), and HOBT (0.10 g, 0.76 mmol) was stirred in 3 mL of DMF at 20°C for 20 h. Water was added and the mixture was extracted with EtOAc. The organic phase was washed successively with 1N aqueous HCl, brine, saturated aqueous NaHCO<sub>3</sub>, and brine and was dried over MgSO<sub>4</sub>. Evaporation of the solvent and purification by preparative TLC, eluting with 1:1 ether:hexanes, gave Compound 1k (0.100 g, 50% yield). MS: *m/z* 524.2 (M + H)<sup>+</sup>.

**G. Cpd 1: (2E)-N,N-Diethyl-3-[3-(4-methoxyphenoxy)-4-[(2S)-pyrrolidin-2-ylmethyl]amino}phenyl]prop-2-enamide.** A mixture of Compound 1k (0.026 g, 0.050 mmol), TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 4 h. After concentration, the residue was purified by reverse phase HPLC to afford Cpd 1 as a TFA salt (0.0063 g, 19% yield). MS: *m/z* 424.2 (M + H)<sup>+</sup>.

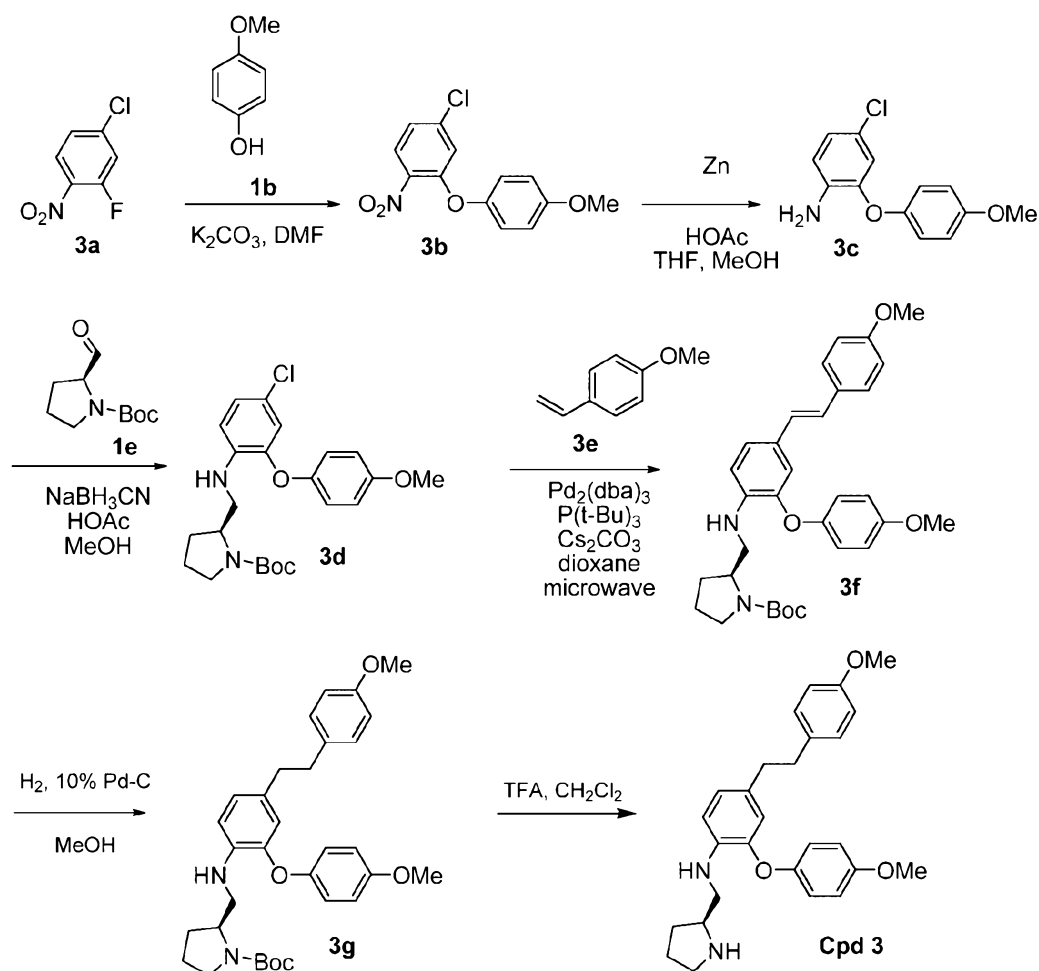
### Example 2



**A. 2-(S)-{[4-(2-Diethylcarbamoyl-ethyl)-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (2a).** A mixture of compound **1k** (0.050 g, 1.0 mmol) and 10% palladium on carbon in MeOH was shaken under a hydrogen atmosphere (34 psi) at 20°C for 4 h. The catalyst was filtered and  
5 solvent was removed by evaporation to give Compound **2a**. MS:  $m/z$  526.3 (M + H)<sup>+</sup>.

**B. Cpd 2: N,N-Diethyl-3-[3-(4-methoxyphenoxy)-4-[(2S)-pyrrolidin-2-ylmethyl]amino}phenyl]propanamide.** A mixture of Compound **2a** (0.050 g, 0.095 mmol), TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 4 h. After concentration, the residue was purified by reverse phase HPLC to afford **Cpd 2** as a TFA salt (0.022 g, 36% yield). <sup>1</sup>H  
10 NMR (300 MHz, CD<sub>3</sub>OD):  $\delta$  6.87-6.91 (m, 5H), 6.78 (d, 1H), 6.60 (d, 1H), 3.90 (m, 1H), 3.79 (s, 3H), 3.42-3.48 (m, 2H) 3.24-3.34 (m, 6H), 2.77 (t, 2H), 2.53 (t, 2H), 2.18-2.28 (m, 1H), 2.00-2.14 (m, 2H), 1.73-1.86 (m, 1H), 1.03-1.08 (m, 6H); MS:  $m/z$  426.3 (M + H)<sup>+</sup>..

## Example 3



**A. 4-Chloro-2-(4-methoxy-phenoxy)nitrobenzene (3b).** 4-Chloro-2-fluoronitrobenzene (Compound **3a**, 1.76 g, 10 mmol), Compound **1b** (1.30 g, 10.5 mmol), and  $K_2CO_3$  (1.52 g, 11 mmol) were heated in 6 mL of DMF at 75°C for 3 h. The mixture was concentrated *in vacuo* and the residue was partitioned between EtOAc and water. The organic layer was washed successively with 1N aqueous NaOH, 1N aqueous HCl, saturated aqueous  $NaHCO_3$ , and brine and dried over  $Na_2SO_4$ . Concentration and purification by flash column chromatography ( $SiO_2$ ), eluting with a hexanes-EtOAc gradient, afforded Compound **3b** as a yellow solid (2.75 g, 98% yield) MS:  $m/z$  279.9 (M + H)<sup>+</sup>.

**B. 4-Chloro-2-(4-methoxy-phenoxy)-aniline (3c).** A mixture of Compound **3b** (2.47 g, 8.83 mmol), zinc (3.46 g, 53 mmol), 60 mL of HOAc, 5 mL of THF, and 36 mL of MeOH was stirred at 20°C for 20 h. The solid material was filtered and washed with MeOH. The filtrate was partitioned between EtOAc and 1N aqueous NaOH. The organic phase was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give Compound **3c** as a black gel that was used without purification (1.80 g, 82% yield). MS: *m/z* 249.9 (M + H)<sup>+</sup>.

**C. 2-(S)-{[4-Chloro-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3d).** NaBH<sub>3</sub>CN (0.95 g, 14.4 mmol) was added to a mixture of Compound **3c** (1.80 g, 7.2 mmol) and Compound **1e** (1.48 g, 7.2 mmol) in 28 mL of MeOH and 3.5 mL of HOAc. The mixture was stirred at 20°C for 1 h. After evaporation of solvent, the residue was extracted with EtOAc. The organic layer was washed successively with saturated aqueous NaHCO<sub>3</sub> and brine and was dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration and purification by flash column chromatography (SiO<sub>2</sub>), eluting with 3:7 EtOAc:hexanes, afforded Compound **3d** as a brown oil (2.84 g, 91% yield). MS: *m/z* 433.1 (M + H)<sup>+</sup>.

**D. (E)-2-(S)-({2-(4-Methoxy-phenoxy)-4-[2-(4-methoxy-phenyl)-ethenyl]-phenylamino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3f).** A mixture of Compound **3d** (0.11 g, 0.254 mmol), 4-vinylanisole (Compound **3e**, 0.042 g, 0.042 mL, 0.305 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (0.035 g, 0.038 mmol), P(*t*Bu)<sub>3</sub> (0.032 g, 0.04 mL, 0.152 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.091 g, 0.279 mmol), and 0.2 mL of dioxane was irradiated in a microwave reactor at 180°C for 30 min. Brine was added and the mixture was extracted with EtOAc. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated, and the residue was purified by preparative TLC to give Compound **3f** (0.05 g, 51% yield). MS: *m/z* 531.4 (M + H)<sup>+</sup>.

**E. (E)-2-(S)-({2-(4-Methoxy-phenoxy)-4-[2-(4-methoxy-phenyl)-ethyl]-phenylamino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (3g).** A mixture of compound **3f** (0.050 g, 0.094 mmol) and 10% palladium on carbon in MeOH was shaken under a hydrogen atmosphere (38 psi) at 20°C. The catalyst was filtered and solvent was removed by evaporation to give Compound **3g** (0.05 g, 100% yield).

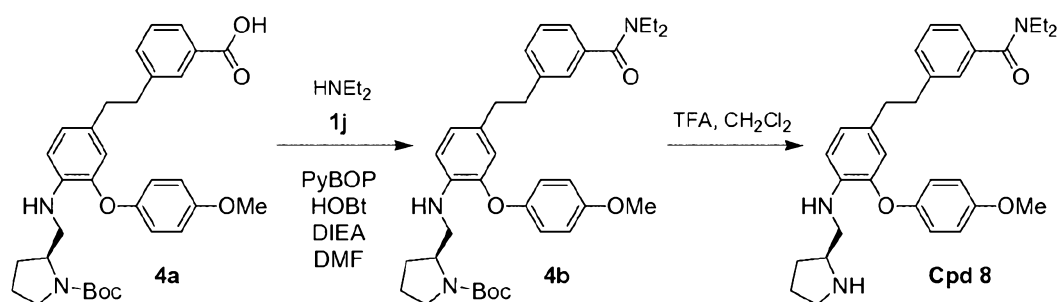


**F. Cpd 3: (S)-{2-(4-Methoxy-phenoxy)-4-[2-(4-methoxy-phenyl)-ethyl]-phenyl}-pyrrolidin-2-ylmethyl-amine.** A mixture of Compound **3g** (0.050 g, 0.094 mmol), TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 2 h. After concentration, the residue was dissolved in CH<sub>3</sub>CN and purified by reverse phase HPLC to afford **Cpd 3** as a TFA salt (0.018 g, 29% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 6.72-6.94 (m, 10H), 6.38 (m, 1H), 3.81-3.92 (m, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.21-3.44 (m, 4H), 2.69-2.71 (m, 4H), 1.98-2.28 (m, 3H), 1.71-1.82 (m, 1H),; MS: *m/z* 432.9 (M + H)<sup>+</sup>.

Following the procedure described above for Example 3 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compounds of the present invention were prepared:

Cpd	MS (M + H) <sup>+</sup>	<sup>1</sup> H NMR
4	433.2	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.05-7.11 (m, 1H), 6.49-6.90 (m, 9H), 6.42 (m, 1H), 3.80-3.92 (m, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.21-3.52 (m, 4H), 2.73-2.79 (m, 4H), 1.91-2.28 (m, 3H), 1.72-1.80 (m, 1H)
5	402.9	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.05-7.18 (m, 5H), 6.52-6.86 (m, 6H), 6.44 (m, 1H), 3.80-3.90 (m, 1H), 3.78 (s, 3H), 3.26-3.45 (m, 4H), 2.73-2.77 (m, 4H), 1.92-2.26 (m, 3H), 1.72-1.80 (m, 1H)
6	421.2	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 6.72-7.08 (m, 10H), 6.38 (m, 1H), 3.81-3.91 (m, 1H), 3.79 (s, 3H), 3.24-3.46 (m, 4H), 2.77-2.79 (m, 4H), 1.96-2.28 (m, 3H), 1.73-1.81 (m, 1H)
7	421.2	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.14-7.22 (m, 1H), 6.72-6.89 (m, 9H), 6.42 (m, 1H), 3.80-3.92 (m, 1H), 3.78 (s, 3H), 3.25-3.46 (m, 4H), 2.75-2.82 (m, 4H), 1.94-2.25 (m, 3H), 1.72-1.79 (m, 1H)

## Example 4

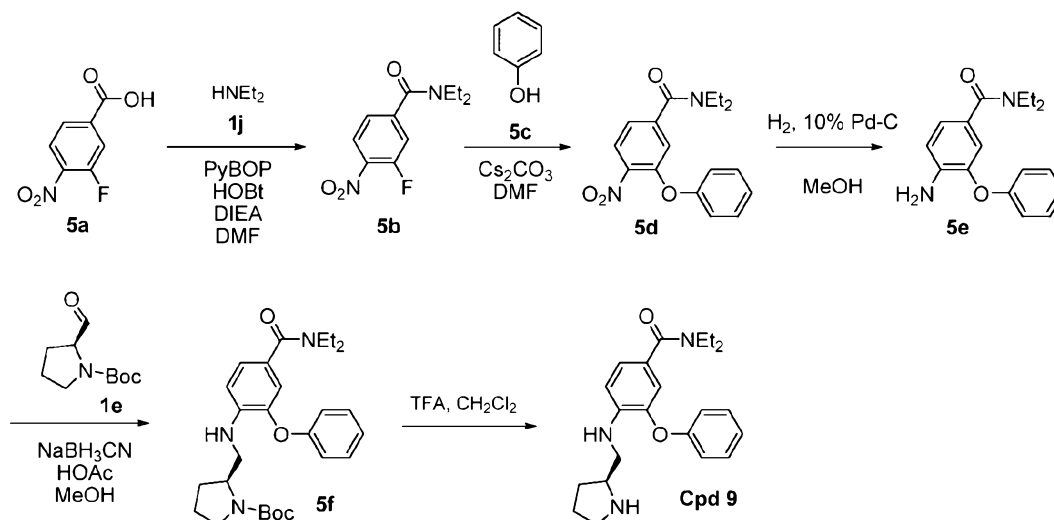


**A. 2-(S)-{[4-[2-(3-Carboxy-phenyl)-ethyl]-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4a).** Compound 4a was prepared according to the method used to prepare Compound 3g described in Example 3 above, substituting 3-ethenylbenzoic acid for Compound 3e. MS:  $m/z$  547.2 ( $M + H$ )<sup>+</sup>.

**B. 2-(S)-{[4-[2-(3-Diethylcarbamoyl-phenyl)-ethyl]-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (4b).** A mixture of Compound 4b (0.016 g, 0.029 mmol), Compound 1j (0.0021 g, 0.003 mL, 0.029 mmol), PyBOP (0.030 g, 0.058 mmol), HOBT (0.0059 g, 0.044 mmol), DIEA (0.0075 g, 0.010 mL, 0.058 mmol), and 1 mL of DMF was stirred at 20°C for 3 h. Water was added and the mixture was extracted with EtOAc. The organic layer was washed successively with 1N aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, and brine and was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of solvent and purification by preparative TLC, eluting with 3:7 EtOAc:hexanes, afforded Compound 4b. MS:  $m/z$  602.3 ( $M + H$ )<sup>+</sup>.

**C. Cpd 8: (S)-N,N-Diethyl-3-(2-{3-(4-methoxy-phenoxy)-4-[(pyrrolidin-2-ylmethyl)-amino]-phenyl}-ethyl)-benzamide.** A mixture of Compound 4b, TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 1.5 h. After concentration, the residue was dissolved in CH<sub>3</sub>CN and purified by reverse phase HPLC to afford Cpd 8 as a TFA salt (0.002 g, 9% yield, steps B and C). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.25-7.33 (m, 2H), 7.12-7.17 (m, 2H), 7.03 (m, 1H), 6.74-6.86 (m, 5H), 6.43 (m, 1H), 3.82-3.90 (m, 1H), 3.77 (s, 3H), 3.38-3.57 (m, 4H), 3.13-3.31 (m, 4H), 2.76-2.86 (m, 4H), 2.00-2.28 (m, 3H), 1.75-1.82 (m, 1H), 1.21-1.26 (m, 3H), 0.98-1.04 (m, 3H); MS:  $m/z$  502.4 ( $M + H$ )<sup>+</sup>.

## Example 5



**A. N,N-Diethyl-4-nitro-3-fluoro-benzamide (5b).** A mixture of Compound **5a** (0.50 g, 2.7 mmol), Compound **1j** (0.20 g, 0.28 mL, 2.7 mmol), PyBOP (2.81 g, 5.4 mmol), HOBT (0.55 g, 4.05 mmol), DIEA (0.70 g, 0.94 mL, 5.4 mmol), and 8 mL of DMF was stirred at 20°C for 3 h. Water was added and the mixture was extracted with EtOAc. The organic layer was washed successively with 1N aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, and brine and was dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of solvent and purification by preparative TLC, eluting with 4:6 EtOAc:hexanes, afforded Compound **5b** (0.67 g, 103% yield). MS: *m/z* 240.9 (M + H)<sup>+</sup>.

**B. N,N-Diethyl-4-nitro-3-phenoxy-benzamide (5d).** Compound **5b** (0.22 g, 0.92 mmol), phenol (Compound **5c**, 0.10 g, 1.1 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.90 g, 2.7 mmol), and 4 mL of DMF were heated with stirring at 120°C for 3 h. Water was added and the resulting mixture was extracted with EtOAc. The organic layer was washed successively with 3N aqueous NaOH, 2N aqueous HCl, and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated. The residue was purified by preparative TLC to provide Compound **5d** as a brown oil. MS: *m/z* 315.0 (M + H)<sup>+</sup>.

**C. 4-Amino-N,N-diethyl-3-phenoxy-benzamide (5e).** A mixture of compound **5d**, prepared in Step B, and 10% palladium on carbon in MeOH was shaken under a

hydrogen atmosphere (30 psi) at 20°C for 3 h. The catalyst was collected by filtration and the solvent was removed by evaporation to give Compound **5e** (0.19 g, 73% yield, steps B and C).

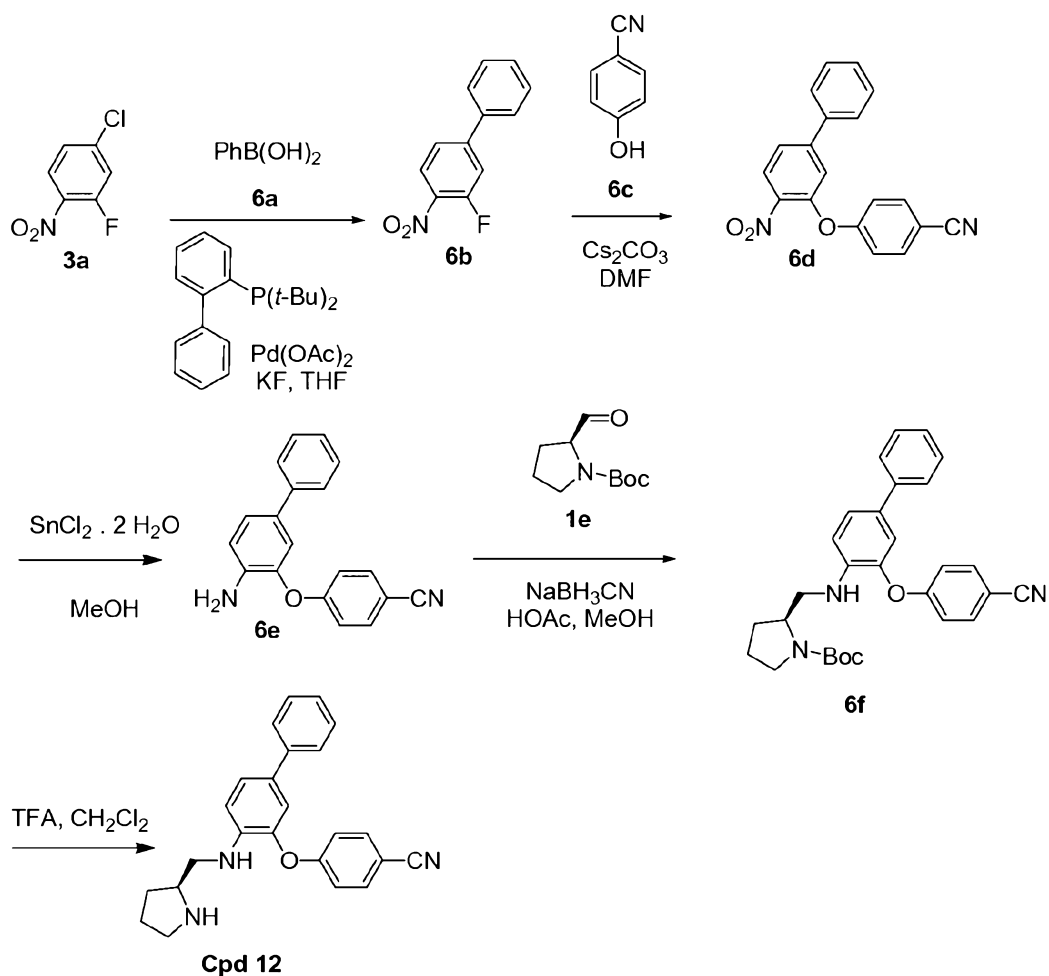
**D. 2-[(4-Diethylcarbamoyl-2-phenoxy-phenylamino)-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (5f).** NaBH<sub>3</sub>CN (0.025 mmol, 0.4 mmol) was added to a mixture of Compound **5e** (0.063 g, 0.2 mmol) and Compound **1e** (0.04 g, 0.2 mmol) in 5 mL of MeOH and 0.4 mL of HOAc. The mixture was stirred at 20°C for 1.5 h. After evaporation of solvent, the residue was extracted with EtOAc. The organic layer was washed successively with saturated aqueous NaHCO<sub>3</sub> and brine and was dried over MgSO<sub>4</sub>. Concentration and purification by preparative TLC afforded Compound **5f** (0.07 g, 75% yield) MS: *m/z* 468.3 (M + H)<sup>+</sup>.

**E. Cpd 9: (S)-N,N-Diethyl-3-phenoxy-4-[(pyrrolidin-2-ylmethyl)-amino]-benzamide.** A mixture of Compound **5f** (0.07 g, 0.15 mmol), TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 1.5 h. After concentration, the residue was dissolved in CH<sub>3</sub>CN and purified by reverse phase HPLC to afford **Cpd 9** as a TFA salt (0.044 g, 49% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.33-7.39 (m, 2H), 7.10-7.15 (m, 2H), 7.00-7.03 (m, 2H), 6.89-6.92 (m, 1H), 6.77 (m, 1H), 3.88-3.93 (m, 1H), 3.26-3.55 (m, 8H), 1.99-2.25 (m, 3H), 1.74-1.81 (m, 1H), 1.03-1.17 (m, 6H); MS: *m/z* 368.0 (M + H)<sup>+</sup>.

Following the procedure described above for Example 5 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compounds of the present invention were prepared:

Cpd	MS (M + H) <sup>+</sup>	<sup>1</sup> H NMR
<b>10</b>	398.0	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 6.66-7.05 (m, 6H), 6.66 (m, 1H), 3.89-3.92 (m, 1H), 3.76 (s, 3H), 3.28-3.56 (m, 8H), 1.99-2.26 (m, 3H), 1.02-1.17 (m, 6H)
<b>11</b>	398.0	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.11-7.21 (m, 2H), 6.97-7.06 (m, 3H), 6.84-6.86 (m, 1H), 6.48 (m, 1H), 3.88-4.00 (m, 1H), 3.77 (s, 3H), 3.54-3.58 (m, 2H), 3.28-3.38 (m, 6H), 2.00-2.27 (m, 3H), 1.81-1.86 (m, 1H), 0.95-1.18 (m, 6H)

## Example 6



**A. 3-Fluoro-4-nitrobiphenyl (6b).** 4-Chloro-2-fluoronitrobenzene (Compound **3a**, 3.51 g, 20 mmol), phenylboronic acid (Compound **6a**, 3.77 g, 30 mmol), potassium fluoride (3.49 g, 60 mmol),  $\text{Pd}(\text{OAc})_2$  (0.045 g, 0.2 mmol), and 2-(di-  
 5 butylphosphino)biphenyl (0.12 g, 0.4 mmol) were added to a dry, nitrogen-swept flask. The flask was evacuated and flushed with nitrogen three times, and THF (25 mL) was added. The reaction mixture was stirred at ambient temperature for 20 h. EtOAc was added and the organic solution was washed successively with 1N aqueous NaOH and  
 10 brine, dried over  $\text{MgSO}_4$ , and concentrated. The crude product was purified by flash column chromatography ( $\text{SiO}_2$ ), eluting with a hexanes-EtOAc gradient to afford pure

Compound **6b** (1.27 g, 30% yield) and an additional quantity of less pure Compound **6b** (3.66 g).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.12-8.18 (m, 1H), 7.47-7.62 (m, 7H).

**B. 4-(4-Nitro-biphenyl-3-yloxy)-benzonitrile (6d).** Compound **6b** (0.22 g, 1.0 mmol), 4-hydroxybenzonitrile (Compound **6c**, 0.19 g, 1.5 mmol),  $\text{Cs}_2\text{CO}_3$  (0.98 g, 3.0 mmol), and 4 mL of DMF were heated with stirring at  $120^\circ\text{C}$  for 3.5 h. The reaction mixture was poured onto water and extracted with EtOAc. The organic layer was washed successively with 3N aqueous NaOH, 2N aqueous HCl, and brine and dried over  $\text{Na}_2\text{SO}_4$ . After removal of solvent, crude Compound **6d** was isolated and used without purification (0.263 g, 83% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.12-8.16 (m, 1H), 7.38-7.66 (m, 9H), 7.06-7.09 (m, 2H).

**C. 4-(4-Amino-biphenyl-3-yloxy)-benzonitrile (6e).** A mixture of compound **6d** (1.0 mmol) and tin (II) chloride dihydrate (1.13 g, 5 mmol) in 10 mL of MeOH was refluxed for 2.5 h. After cooling to room temperature, solvent was removed by evaporation and the residue was mixed with water. The aqueous solution was adjusted to pH 9 using saturated aqueous  $\text{NaHCO}_3$  and the mixture was extracted with EtOAc. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and evaporated to give Compound **6e** as a brown solid that was used without purification. MS:  $m/z$  287.2 ( $\text{M} + \text{H}$ ) $^+$ .

**D. 2-(S)-{[3-(4-Cyano-phenoxy)-biphenyl-4-ylamino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (6f).**  $\text{NaBH}_3\text{CN}$  (0.066 g, 1.0 mmol) was added to a mixture of Compound **6e** (0.14 g, 0.50 mmol) and Compound **1e** (0.10 g, 0.50 mmol) in 4 mL of MeOH and 0.3 mL of HOAc. The mixture was stirred at  $20^\circ\text{C}$  for 1.5 h. After evaporation of solvent, the residue was extracted with EtOAc. The organic layer was washed successively with saturated aqueous  $\text{NaHCO}_3$  and brine and was dried over  $\text{MgSO}_4$ . Concentration and purification by preparative TLC afforded Compound **6f** as a brown oil (0.167 g, 71% yield). MS:  $m/z$  470.2 ( $\text{M} + \text{H}$ ) $^+$ .

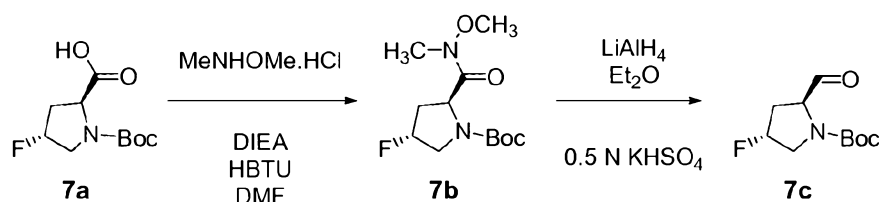
**E. Cpd 12. (S)-4-{4-[(Pyrrolidin-2-ylmethyl)-amino]-biphenyl-3-yloxy}-benzonitrile.** A mixture of Compound **6f** (0.167 g, 0.36 mmol), TFA, and  $\text{CH}_2\text{Cl}_2$  was stirred at  $20^\circ\text{C}$  for 2 h. After concentration, the residue was dissolved in  $\text{CH}_3\text{CN}$  and purified by reverse phase HPLC to afford Cpd **12** as a TFA salt (0.029 g, 13% yield). MS:  $m/z$  370.2 ( $\text{M} + \text{H}$ ) $^+$ .

Following the procedure described above for Example 6 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compounds of the present invention were prepared:

Cpd	MS (M + H) <sup>+</sup>	<sup>1</sup> H NMR
<b>13</b>	370.2	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.18-7.52 (m, 11H), 7.00-7.03 (m, 1H), 3.80-3.90 (m, 1H), 3.48-3.52 (m, 2H), 3.26-3.31 (m, 2H), 2.02-2.24 (m, 3H), 1.75-1.82 (m, 1H)
<b>14</b>	345.1	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.03-7.48 (m, 7H), 7.07-7.12 (m, 1H), 6.95-7.04 (m, 5H), 3.85-3.96 (m, 1H), 3.48-3.54 (m, 2H), 3.26-3.31 (m, 2H), 2.03-2.30 (m, 3H), 1.70-1.84 (m, 1H)
<b>15</b>	375.1	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.44-7.46 (m, 2H), 7.32-7.38 (m, 3H), 7.21-7.24 (m, 2H), 7.10 (m, 1H), 6.95-6.98 (m, 1H), 6.56-6.69 (m, 3H), 3.85-3.96 (m, 1H), 3.76 (s, 3H), 3.48-3.53 (m, 2H), 3.26-3.30 (m, 2H), 1.97-2.30 (m, 3H), 1.73-1.86 (m, 1H)
<b>16</b>	363.0	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.42-7.45 (m, 2H), 7.30-7.37 (m, 3H), 7.21-7.24 (m, 1H), 6.94-7.22 (m, 6H), 3.85-3.96 (m, 1H), 3.48-3.54 (m, 2H), 3.27-3.33 (m, 2H), 1.99-2.32 (m, 3H), 1.74-1.87 (m, 1H)
<b>17</b>	428.9	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 6.97-7.50 (m, 12H), 3.83-3.95 (m, 1H), 3.40-3.53 (m, 2H), 3.27-3.31 (m, 2H), 2.00-2.28 (m, 3H), 1.77-1.82 (m, 2H)
<b>18</b>	412.8	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.53-7.55 (m, 2H), 7.23-7.32 (m, 7H), 6.93-6.96 (m, 1H), 6.46 (m, 1H), 3.95-4.08 (m, 1H), 3.59-3.63 (m, 2H), 3.31-3.36 (m, 2H), 2.09-2.38 (m, 3H), 1.82-1.93 (m, 1H)
<b>19</b>	348.9	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.18-7.40 (m, 6H), 6.89-7.02 (m, 6H), 3.79 (s, 3H), 3.56-3.60 (m, 2H), 3.26-3.30 (m, 2H), 2.74 (s, 3H)
<b>20</b>	402.9	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.98-8.02 (m, 2H), 7.43-7.50 (m, 3H), 7.35-7.37 (m, 2H), 7.19-7.23 (m, 2H), 6.99-7.06 (m, 3H), 3.82-3.94 (m, 1H), 3.87 (s, 3H), 3.48-3.52 (m, 2H), 3.25-3.31 (m, 2H), 1.93-2.28 (m, 3H), 1.71-1.83 (m, 1H)

Cpd	MS (M + H) <sup>+</sup>	<sup>1</sup> H NMR
21	402.9	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.73-7.76 (m, 1H), 7.60 (m, 1H), 7.23-7.50 (m, 8H), 7.13 (m, 1H), 6.99-7.02 (m, 1H), 3.84-3.95 (m, 1H), 3.88 (s, 3H), 3.49-3.54 (m, 2H), 3.26-3.30 (m, 2H), 1.98-2.29 (m, 3H), 1.75-1.83 (m, 1H)
22	412.8	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.56 (m, 1H), 7.18-7.40 (m, 7H), 6.91-6.99 (m, 3H), 3.89-3.95 (m, 1H), 3.53-3.56 (m, 2H), 3.28-3.34 (m, 2H), 2.00-2.27 (m, 3H), 1.76-1.83 (m, 1H)
23	375.0	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.23-7.44 (m, 6H), 6.93-7.10 (m, 6H), 3.76-3.88 (m, 1H), 3.79 (s, 3H), 3.44-3.48 (m, 2H), 3.14-3.18 (m, 2H), 2.25-2.32 (m, 2H), 1.70-1.84 (m, 2H)

### Example 7



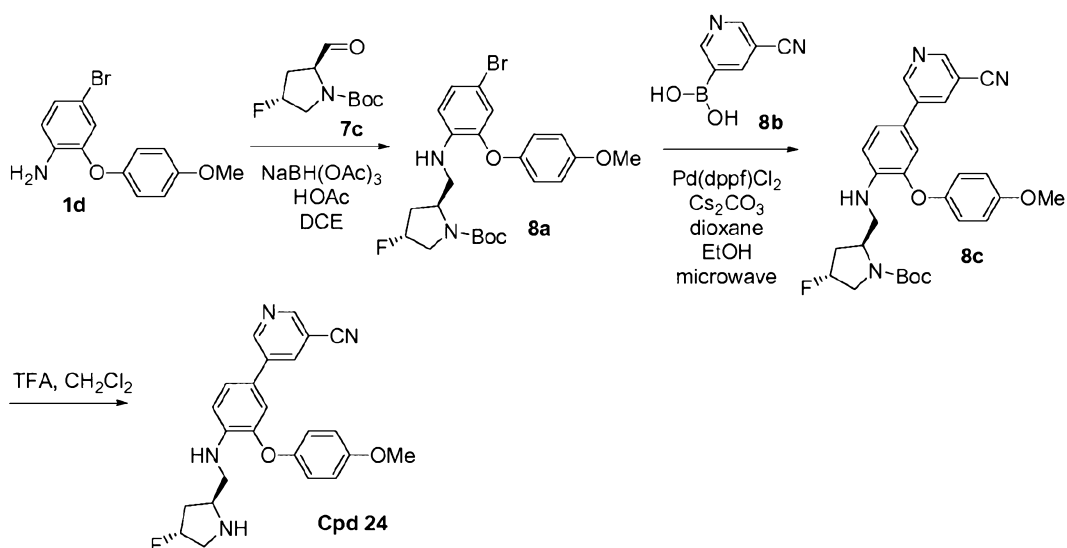
- A. (2S,4R)-4-Fluoro-2-(methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (7b).** HBTU (12.3 g, 32.3 mmol) was added in portions to a solution of Compound 7a (6.26 g, 26.9 mmol), *N,O*-dimethylhydroxylamine hydrochloride (3.15 g, 32.3 mmol), and DIEA (5.62 mL, 4.17 g, 32.3 mmol) in 60 mL of DMF at 0°C. After 15 min, the cooling bath was removed and the mixture was stirred 16 h at 20°C. EtOAc (200 mL) and saturated aqueous NH<sub>4</sub>Cl (100 mL) were added. The organic layer was separated, washed with saturated aqueous NaHCO<sub>3</sub> (100 mL), and brine (100 mL), and dried over MgSO<sub>4</sub>. The solution was concentrated to give 7.7 g of off-white oil that was purified by flash column chromatography (SiO<sub>2</sub>), eluting with 10% MeOH/CH<sub>2</sub>Cl<sub>2</sub>, to yield Compound 7b (5.47 g, 74% yield). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ 5.29 (1H, dt), 4.70 (1H, dd), 3.50 (2H, m), 3.13 (3H, s), 2.69 (3H, s), 2.00 (2H, m), 1.34 (9H, s).



**B. (2S,4R)-4-Fluoro-2-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester**

**(7c).** A 1M solution of LiAlH<sub>4</sub> in Et<sub>2</sub>O (19.2 mL, 19.2 mmol) was added in dropwise to a solution of Compound **7b** (3.54 g, 12.8 mmol) in 10 mL of Et<sub>2</sub>O at 0°C. The mixture was stirred for 1.5 h at 20°C. 10 mL of 0.5 N saturated aqueous KHSO<sub>4</sub> was added, followed by 25 mL of Et<sub>2</sub>O. The organic layer was separated and washed with 1N aqueous NaOH to break up the aluminum complex. The organic layer was separated, dried over MgSO<sub>4</sub>, and concentrated to provide Compound **7c** as an oil (1.33 g, 48% yield). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>): δ 9.45 (1H, s), 5.10 (1H, m), 4.20 (1H, m), 3.50 (2H, m), 2.20 (2H, m), 1.48 (9H, s).

10

**Example 8****A. (2S,4R)-2-([4-Bromo-2-(4-methoxy-phenoxy)-phenylamino]-methyl)-4-fluoro-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**8a**).**

A mixture of Compound **1d** (1.18 g, 4.0 mmol), Compound **7c** (1.33 g, 6.1 mmol), and 5 drops of HOAc in 10 mL of DCE was stirred for 5 min at 20 °C. NaBH(OAc)<sub>3</sub> (2.54 g, 12 mmol) was added in portions over a 5 min period and the mixture was stirred at 20°C for 20 h. Saturated aqueous NH<sub>4</sub>Cl (25 mL) was added to the stirring mixture, followed by 100 mL of CH<sub>2</sub>Cl<sub>2</sub> and 10 mL of water. The organic layer was separated and the aqueous layer was extracted

with 50 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated to give 2 g of crude product. This material was purified by flash column chromatography (SiO<sub>2</sub>), eluting with a hexanes-EtOAc gradient, to yield Compound **8a** (0.496 g, 25% yield). MS: *m/z* 495.0/497.0 (M + H)<sup>+</sup>.

5            **B. (2S,4R)-2-{{4-(5-Cyano-pyridin-3-yl)-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-4-fluoro-pyrrolidine-1-carboxylic acid *tert*-butyl ester (8c).** A mixture of Compound **8a** (0.124 g, 0.30mmol), Compound **8b** (0.096 g, 0.65 mmol), Pd(dppf)Cl<sub>2</sub> (0.055 g, 0.075 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.244 g, 0.75 mmol), 0.25 mL of EtOH, and 1 mL of dioxane was irradiated in a microwave reactor at 140°C for 15 min. The reaction mixture was filtered and the solid was washed with 100 mL of EtOAc. The filtrate was washed with saturated aqueous K<sub>2</sub>CO<sub>3</sub> dried over Na<sub>2</sub>SO<sub>4</sub> and charcoal, and concentrated to afford 0.32 g of crude residue containing Compound **8c**.

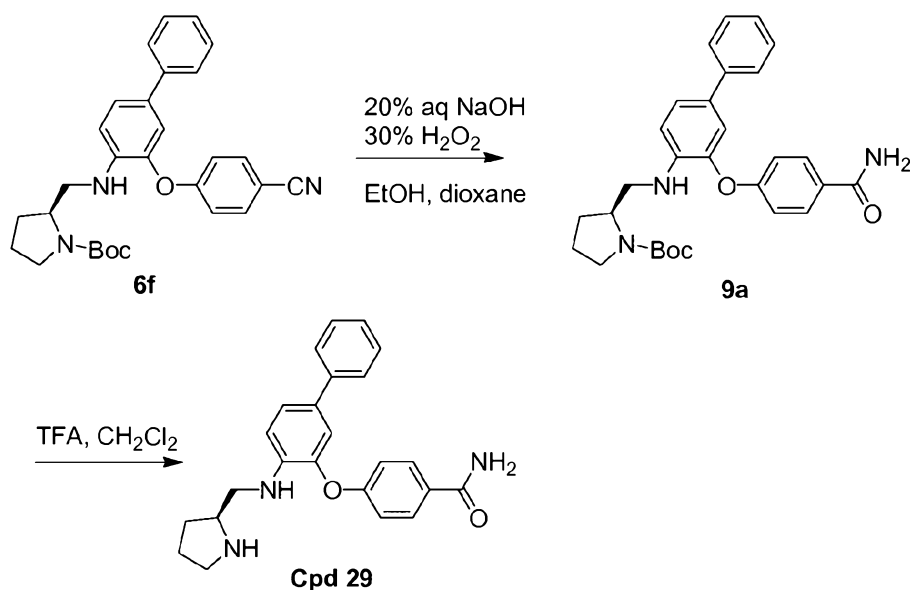
15            **C. Cpd 24: (2S,4R)-5-[4-[(4-Fluoro-pyrrolidin-2-ylmethyl)-amino]-3-(4-methoxy-phenoxy)-phenyl]-nicotinonitrile.** TFA (5 mL) was added dropwise to a solution of the residue from Step B above in 10 mL of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred for 4 h at 20°C and was then evaporated. The residue was purified by reverse phase HPLC to afford **Cpd 24** as a TFA salt (0.058 g, 36% yield for 2 steps). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): 8.76 (1H, d), 8.63 (1H, d), 8.14 (1H, d), 7.31 (1H, dd), 6.98-6.82 (6H, m), 5.37 (1H, d), 4.12 (1H, m), 3.65-3.40 (5H, m), 2.50 (1H, m), 1.95 (1H, m); MS: *m/z* 419.1 (M + H)<sup>+</sup>.

Following the procedure described above for Example 8 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compounds of the present invention were prepared:

Cpd	MS (M + H) <sup>+</sup>	<sup>1</sup> H NMR
<b>25</b>	412.0	
<b>26</b>	440.1	

Cpd	MS (M + H) <sup>+</sup>	<sup>1</sup> H NMR
27	424.3	<sup>1</sup> H NMR (400-MHz, CDCl <sub>3</sub> ): δ 8.44 (s, 1H); 8.33 (s, 1H); 7.86 (s, 1H); 7.33 (s, 1H); 6.95 (m, 1H); 4.11 (m, 2H); 3.8 (s, 6H); 3.4 (m, 1H); 2.55 (m, 2H); 2.24-2.01 (m, 2H); 1.24 (m, 1H)
28	408.3	<sup>1</sup> H NMR (400-MHz, CDCl <sub>3</sub> ): δ 8.7 (s, 1H); 8.5 (m, 2H); 7.5 (s, 1H); 7.2-6.9 (m, 6H); 4.2 (m, 1H); 3.7 (s, 3H); 3.7 (m, 3H); 3.5 (m, 1H); 2.85 (m, 3H); 2.56 (s, 3H)

### Example 9



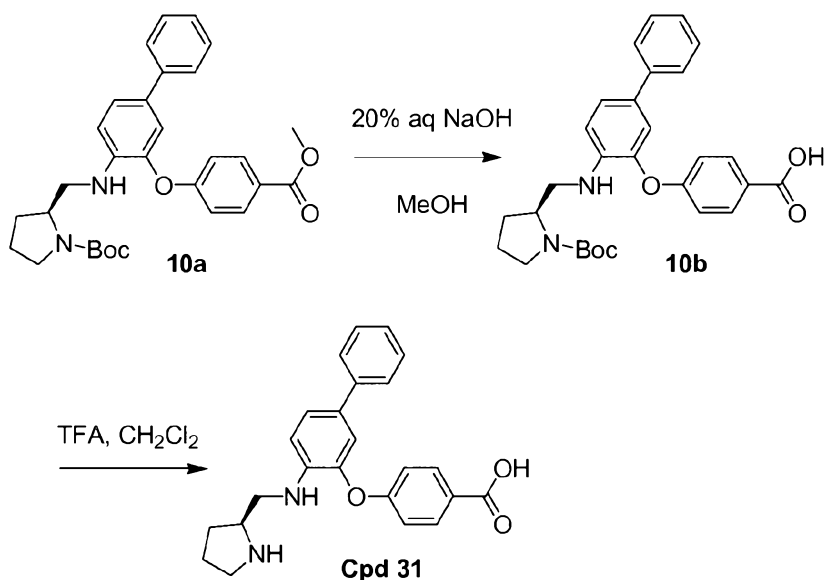
- A. 2-(S)-{[3-(4-Carbamoyl-phenoxy)-biphenyl-4-ylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**9a**).** 20% aqueous NaOH (0.5 mL) and 30% aqueous H<sub>2</sub>O<sub>2</sub> (0.4 mL) were added to a solution of compound **6f** (0.040 g, 0.085 mmol) in 1.5 mL of EtOH and 1.5 mL of dioxane. The mixture was heated at 60°C for 2 days. The reaction mixture was extracted with EtOAc, dried over MgSO<sub>4</sub>, and concentrated to give Compound **9a**. MS: *m/z* 488.3 (M + H)<sup>+</sup>.
- B. Cpd 29: (S)-4-[4-[(Pyrrolidin-2-ylmethyl)-amino]-biphenyl-3-yloxy]-benzamide.** A mixture of Compound **9a**, TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 2 h.

After concentration, the residue was dissolved in CH<sub>3</sub>CN and purified by reverse phase HPLC to afford **Cpd 29** as a TFA salt (0.015 g, 29% yield for 2 steps). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.87-7.89 (m, 2H), 7.33-7.49 (m, 5H), 7.18-7.19 (m, 2H), 7.00-7.06 (m, 3H), 3.84-3.95 (m, 1H), 3.44-3.57 (m, 2H), 3.28-3.35 (m, 2H), 1.98-2.28 (m, 3H), 1.72-1.82 (m, 1H); MS: *m/z* 387.9 (M + H)<sup>+</sup>.

Following the procedure described above for Example 9 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compound of the present invention was prepared:

Cpd	MS (M + H) <sup>+</sup>	<sup>1</sup> H NMR
<b>30</b>	387.9	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.55-7.58 (m, 1H), 7.31-7.49 (m, 7H), 7.14-7.23 (m, 3H), 6.98-7.00 (m, 1H), 3.85-3.96 (m, 1H), 3.43-3.58 (m, 2H), 3.25-3.31 (m, 2H), 1.98-2.27 (m, 3H), 1.73-1.84 (m, 1H)

### Example 10



**A. 2-(S)-{[3-(4-Methoxycarbonyl-phenoxy)-biphenyl-4-ylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (10a).** Compound **10a** was prepared

according to the method used to prepare Compound **6f** described in Example 6 above, substituting methyl 4-hydroxybenzoate for Compound **6c**. MS:  $m/z$  503.2 ( $M + H$ )<sup>+</sup>.

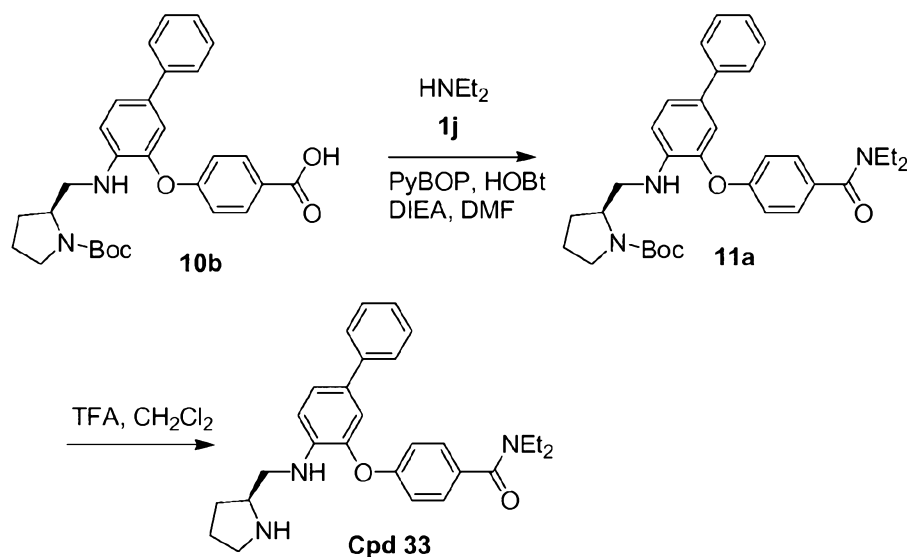
**B. 2-(S)-{[3-(4-Carboxy-phenoxy)-biphenyl-4-ylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**10b**).** A mixture of Compound **10a** (0.034 g, 0.068 mmol), 20% aqueous NaOH, and MeOH was stirred at 20°C for 20 h. After evaporation of the MeOH, the aqueous phase was acidified and extracted with EtOAc. The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated to give Compound **10b** (0.032 g, 95% yield). MS:  $m/z$  489.2 ( $M + H$ )<sup>+</sup>.

**C. Cpd 31: (S)-4-{4-[(Pyrrolidin-2-ylmethyl)-amino]-biphenyl-3-yloxy}-benzoic acid.** A mixture of Compound **10b** (0.032 g, 0.065 mmol), TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 2 h. After concentration, the residue was dissolved in CH<sub>3</sub>CN and purified by reverse phase HPLC to afford **Cpd 31** as a TFA salt (0.019 g, 47% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.98-8.13 (m, 2H), 7.43-7.50 (m, 3H), 7.32-7.37 (m, 2H), 7.20-7.25 (m, 2H), 6.99-7.05 (m, 3H), 3.83-3.96 (m, 1H), 3.42-3.58 (m, 2H), 3.25-3.30 (m, 2H), 1.95-2.28 (m, 3H), 1.70-1.83 (m, 1H) : MS:  $m/z$  389.0 ( $M + H$ )<sup>+</sup>.

Following the procedure described above for Example 10 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compound of the present invention was prepared:

Cpd	MS ( $M + H$ ) <sup>+</sup>	<sup>1</sup> H NMR
<b>32</b>	389.0	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.74-7.79 (m, 1H), 7.61-7.62 (m, 1H), 7.14-7.48 (m, 9H), 6.97-7.00 (m, 1H), 3.87-3.90 (m, 1H), 3.49-3.53 (m, 2H), 3.25-3.32 (m, 2H), 1.99-2.22 (m, 3H), 1.73-1.80 (m, 1H)

## Example 11



**A. 2-(S)-{[3-(4-Diethylcarbamoyl-phenoxy)-biphenyl-4-ylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (11a).** A mixture of Compound **10b** (0.021 g, 0.043 mmol), Compound **1j** (0.0094 g, 0.0013 mL, 0.129 mmol), PyBOP (0.045 g, 0.086 mmol), HOBT (0.0087 g, 0.065 mmol), DIEA (0.011 g, 0.015 mL, 0.086 mmol), and 1 mL of DMF was stirred at 20°C for 3 h. Water was added and the mixture was extracted with EtOAc. The organic layer was washed successively with 1N aqueous HCl, saturated aqueous NaHCO<sub>3</sub>, and brine and was dried over MgSO<sub>4</sub>. Evaporation of solvent and purification by reverse phase HPLC gave Compound **11a**. MS: *m/z* 544.3 (M + H)<sup>+</sup>.

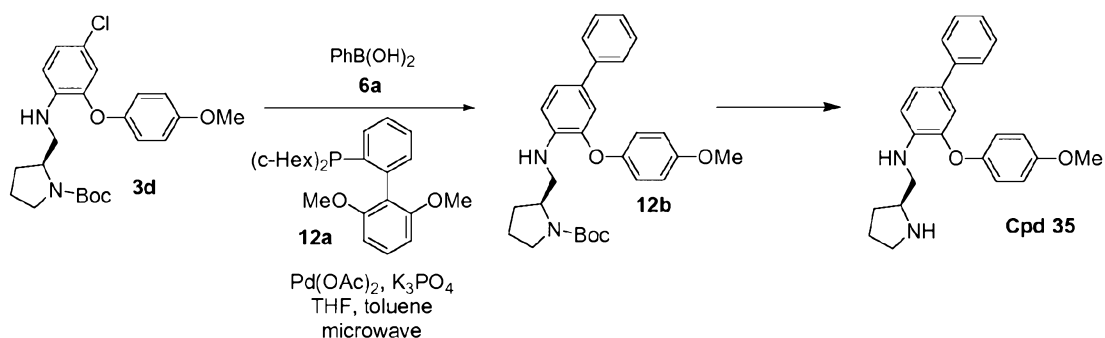
**B. Cpd 33: (S)-N,N-Diethyl-4-{4-[(pyrrolidin-2-ylmethyl)-amino]-biphenyl-3-yloxy}-benzamide.** A mixture of Compound **11a**, TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 2 h. After concentration, the residue was dissolved in CH<sub>3</sub>CN and purified by reverse phase HPLC to afford **Cpd 33** as a TFA salt (0.016 g, 55% yield for 2 steps). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.32-7.50 (m, 7H), 7.23-7.25 (m, 1H), 7.16 (m, 1H), 7.05-7.09 (m, 2H), 6.98-7.01 (m, 1H), 3.87-3.91 (m, 1H), 3.44-3.56 (m, 4H), 3.26-3.35 (m, 4H), 2.02-2.23 (m, 3H), 1.74-1.81 (m, 1H), 1.09-1.28 (m, 6H); MS: *m/z* 444.0 (M + H)<sup>+</sup>.

Following the procedure described above for Example 11 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compound of the present invention was prepared:

Cpd	MS (M + H) <sup>+</sup>	<sup>1</sup> H NMR
34	444.0	<sup>1</sup> H NMR (300 MHz, CD <sub>3</sub> OD): δ 7.31-7.48 (m, 6H), 6.88-7.24 (m, 6H), 3.87-3.92 (m, 1H), 3.42-3.58 (m, 4H), 3.22-3.32 (m, 4H), 2.19-2.25 (m, 1H), 2.01-2.08 (m, 2H), 1.73-1.80 (m, 1H), 1.17-1.22 (m, 3H), 1.00-1.04 (m, 3H)

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### Example 12



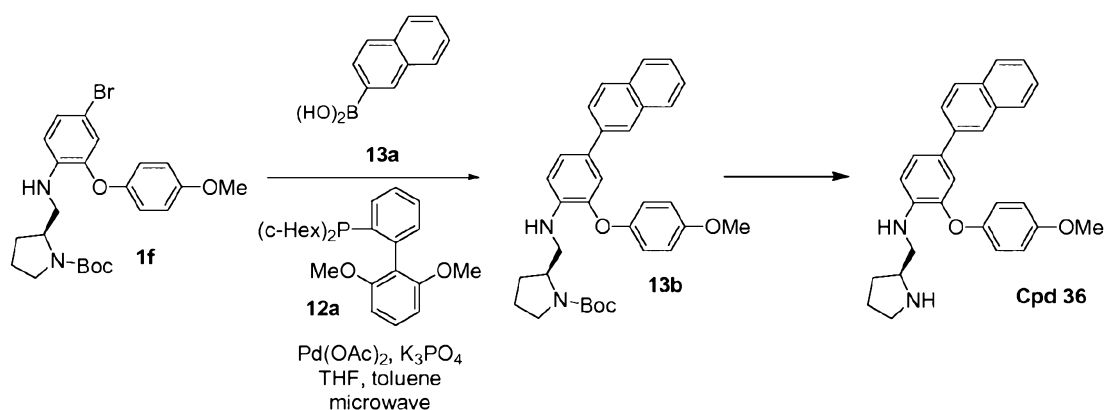
**A. 2-(S)-[3-(4-Methoxy-phenoxy)-biphenyl-4-ylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (12b).** A microwave reaction vessel containing a mixture of Compound 3d (0.070 g, 0.16 mmol), Compound 6a (0.030 g, 0.24 mmol), Pd(OAc)<sub>2</sub> (0.0034 g, 0.015 mmol), Compound 12a (0.016 g, 0.039 mmol), and K<sub>3</sub>PO<sub>4</sub> (0.064 g, 0.30 mmol) was evacuated and flushed with nitrogen three times. Toluene (0.5 mL) and THF (0.3 mL) were added and the mixture was irradiated in a microwave reactor at 160°C for 30 min. The reaction mixture was filtered and the concentrated filtrate was purified by preparative TLC to give Compound 12b (0.050 g, 66% yield). MS: *m/z* 475.2 (M + H)<sup>+</sup>.

**B. Cpd 35: (S)-[3-(4-Methoxy-phenoxy)-biphenyl-4-yl]-pyrrolidin-2-ylmethyl-amine.** A mixture of Compound 12b (0.050 g, 0.11 mmol), TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 1 h. After concentration, the residue was dissolved in CH<sub>3</sub>CN and purified by

reverse phase HPLC to afford **Cpd 35** as a TFA salt (0.0063 g, 9% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  6.68-7.50 (m, 12H), 4.08-4.14 (m, 1H), 3.78-3.83 (m, 1H), 3.80 (s, 3H), 3.56-3.61 (m, 1H), 3.32-3.41 (m, 2H), 2.00-2.27 (m, 3H), 1.77-1.88 (m, 1H); MS:  $m/z$  375.1 ( $\text{M} + \text{H}$ ) $^+$ .

5

### Example 13



**A. 2-(S)-{[2-(4-Methoxy-phenoxy)-4-naphthalen-2-yl-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**13b**).** A mixture of Compound **1f** (0.14 g, 0.30 mmol), Compound **13a** (0.077 g, 0.45 mmol),  $\text{Pd}_2(\text{dba})_3$  (0.0011 g, 0.012 mmol), Compound **12a** (0.010 g, 0.024 mmol),  $\text{K}_3\text{PO}_4$  (0.13 g, 0.60 mmol), and 0.6 mL of toluene was irradiated in a microwave reactor at 160°C for 30 min. The reaction mixture was filtered and the concentrated filtrate was purified by preparative TLC to give Compound **13b**. MS:  $m/z$  425.2 ( $\text{M} - \text{Boc}$ ) $^+$ .

**B. Cpd 36: (S)-[2-(4-Methoxy-phenoxy)-4-naphthalen-2-yl-phenyl]-pyrrolidin-2-ylmethyl-amine.** A mixture of Compound **13b**, TFA, and  $\text{CH}_2\text{Cl}_2$  was stirred at 20°C for 1.5 h. After concentration, the residue was dissolved in  $\text{CH}_3\text{CN}$  and purified by reverse phase HPLC to afford **Cpd 36** as a TFA salt (0.0084 g, 3% yield for 2 steps).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.78-7.81 (m, 4H), 7.32-7.55 (m, 4H), 7.11 (m, 1H), 6.83-6.99 (m, 5H), 3.84-3.95 (m, 1H), 3.7 (s, 3H), 3.50-3.70 (m, 2H), 3.26 (m, 2H), 1.98-2.23 (m, 3H), 1.73-1.83 (m, 1H); MS:  $m/z$  425.0 ( $\text{M} + \text{H}$ ) $^+$ .

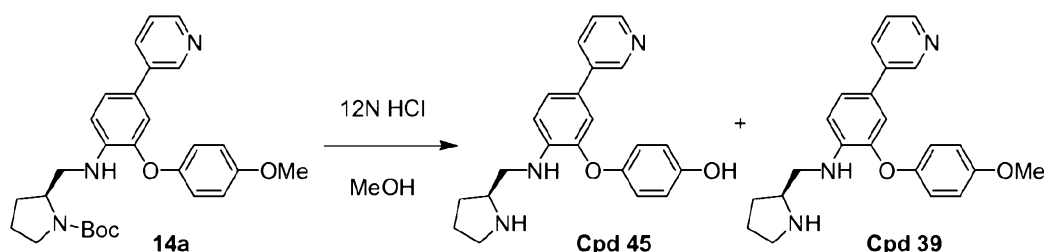
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Following the procedure described above for Example 13 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compounds of the present invention were prepared:

<b>Cpd</b>	<b>MS (M + H)<sup>+</sup></b>	<b><sup>1</sup>H NMR</b>
<b>37</b>	424.9	<sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ): δ 7.75-7.92 (m, 3H), 7.28-7.47 (m, 4H), 7.09-7.25 (m, 1H), 6.68-6.78 (m, 6H), 3.84-3.95 (m, 1H), 3.73 (s, 3H), 3.53-3.67 (m, 2H), 3.18-3.26 (m, 2H), 1.79-2.23 (m, 4H).
<b>38</b>	375.9	<sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ): δ 8.44-8.47 (m, 2H), 7.45-7.48 (m, 2H), 7.25-7.29 (m, 1H), 6.75-6.91 (m, 6H), 3.74-4.10 (m, 5H), 3.34-3.61 (m, 3H), 2.13-2.30 (m, 3H), 1.84-1.93 (m, 1H).
<b>39</b>	375.9	<sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ): δ 8.59-8.69 (m, 2H), 8.14-8.17 (m, 1H), 7.74-7.79 (m, 1H), 7.12-7.16 (m, 1H), 6.83 (s, 4H), 6.68-6.75 (m, 2H), 3.97-4.09 (m, 1H), 3.78 (s, 3H), 3.30-3.70 (m, 4H), 2.07-2.28 (m, 3H), 1.84-1.88 (m, 1H).
<b>40</b>	365.0	<sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ): δ 6.50-7.54 (m, 10H), 4.02-4.18 (m, 1H), 3.80 (s, 3H), 3.74-3.79 (m, 1H), 3.26-3.58 (m, 3H), 2.02-2.26 (m, 3H), 1.79-1.84 (m, 1H).
<b>41</b>	380.9	<sup>1</sup> H NMR (300 MHz, CDCl <sub>3</sub> ): δ 7.17-7.30 (m, 4H), 6.77-6.96 (m, 6H), 3.82-3.94 (m, 1H), 3.77 (s, 3H), 3.43-3.63 (m, 2H), 3.14-3.26 (m, 2H), 1.94-2.19 (m, 3H), 1.70-1.82 (m, 1H).
<b>42</b>	377.2	
<b>43</b>	394.2	
<b>44</b>	401.1	

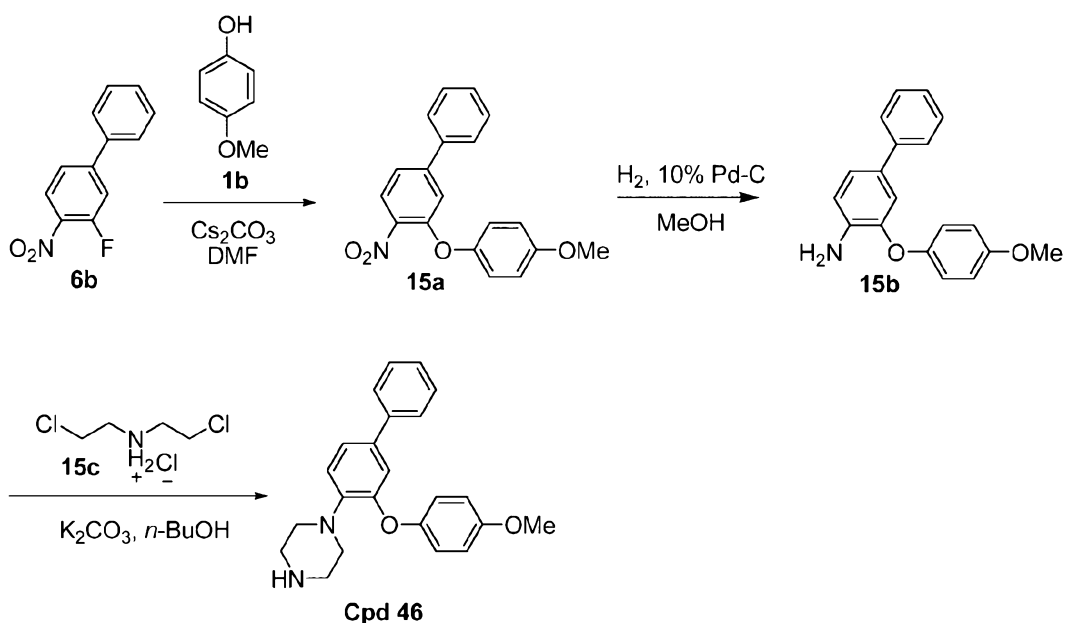
## Example 14



**A. 2-([2-(4-methoxyphenoxy)-4-pyridin-3-ylphenylamino]-methyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (14a).** Compound **14a** was prepared according to the method described in Example 13 above, substituting pyridine-3-boronic acid for Compound **13a**. MS:  $m/z$  476.3 ( $M + H$ )<sup>+</sup>.

**B. Cpd 45: (S)-4-{5-Pyridin-3-yl-2-[(pyrrolidin-2-ylmethyl)-amino]-phenoxy}-phenol.** A mixture of Compound **14a** (0.18 g, 0.38 mmol), 2 mL of concentrated (12 N) HCl, and 2 mL of MeOH was stirred at 20°C for 3 h. After concentration, the residue was purified by preparative TLC, eluting with MeOH:CH<sub>2</sub>Cl<sub>2</sub>. The product was taken up in MeOH, filtered, and concentrated to give a yellow solid. This material was neutralized with saturated aqueous NaHCO<sub>3</sub> and extracted into EtOAc. The organic phase was washed with water, concentrated to a small volume, filtered through a 0.4 μm filter disk, and acidified with 2N aqueous HCl. The EtOAc was evaporated and the residue was dissolved in water, filtered, and lyophilized. The resulting material was purified by reverse phase HPLC. The fractions containing **Cpd 39** were concentrated, neutralized with saturated aqueous NaHCO<sub>3</sub>, and extracted with EtOAc. The organic phase was washed with water and concentrated; the residue was dissolved in dilute aqueous HCl, filtered, and lyophilized to give **Cpd 39** as an HCl salt (0.195 g, ). The fractions containing **Cpd 45** were concentrated and lyophilized to give **Cpd 45** as a TFA salt (0.013 g). MS:  $m/z$  362.2 ( $M + H$ )<sup>+</sup>.

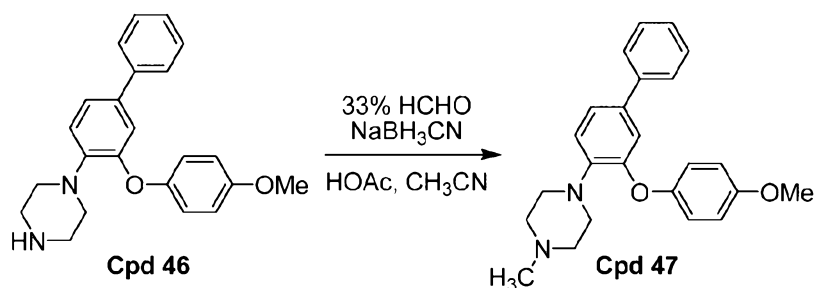
## Example 15



- A. 3-(4-Methoxy-phenoxy)-4-nitrobiphenyl (15a).** Compound **6b** (0.22 g, 1.0 mmol), Compound **1b** (0.19 g, 1.5 mmol),  $\text{Cs}_2\text{CO}_3$  (0.98 g, 3.0 mmol), and 4 mL of DMF were heated with stirring at 120°C for 3 h. The reaction mixture was poured onto ice water and the resulting solid was collected by filtration. The solid was dissolved in EtOAc and dried over  $\text{Na}_2\text{SO}_4$ . After removal of solvent, Compound **15a** was isolated as a brown oil that was used without purification (0.45 g, ~140% yield).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.02 (m, 1H), 7.32-7.47 (m, 6H), 7.06-7.10 (m, 3H), 6.91-6.94 (m, 2H), 3.82 (s, 3H).
- B. 3-(4-Methoxy-phenoxy)-biphenyl-4-ylamine (15b).** A mixture of compound **15a** (~1.0 mmol) and 10% palladium on carbon in MeOH was shaken under a hydrogen atmosphere (34 psi) at 20°C for 3 h. The catalyst was filtered and solvent was removed by evaporation to give Compound **15b** as a brown oil that was used without purification (0.33 g, 113% yield). MS:  $m/z$  292.2 ( $\text{M} + \text{H}^+$ ).
- C. Cpd 46: 1-[3-(4-Methoxy-phenoxy)biphenyl-4-yl]piperazine.** A mixture of Compound **15b** (0.16 g, 0.55 mmol), bis-(2-chloroethyl)ammonium chloride (Compound **15c**, 0.10 g, 0.55 mmol),  $\text{K}_2\text{CO}_3$  (0.038 g, 0.275 mmol) and 2 mL of *n*-butanol was heated at reflux for 42 h. After cooling to room temperature, brine was added and the mixture

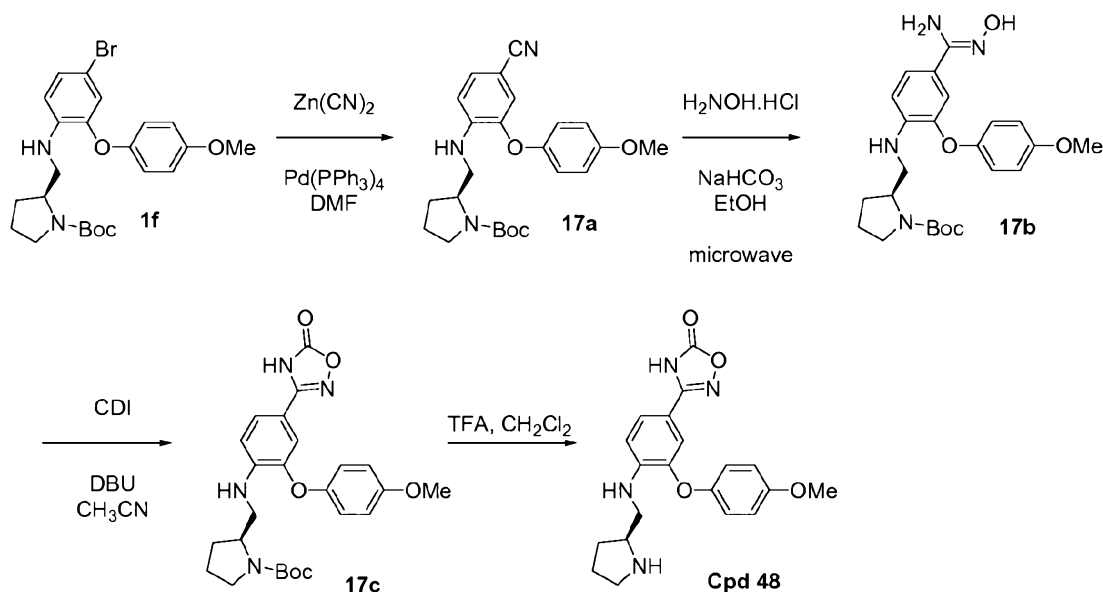
was extracted with EtOAc. The organic layer was dried over  $\text{MgSO}_4$  and concentrated to give crude residue that was purified by reverse phase HPLC to afford **Cpd 46** as a TFA salt.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.47-7.50 (m, 2H), 7.37-7.41 (m, 3H), 7.28-7.31 (m, 1H), 7.12-7.19 (m, 2H), 6.92-6.94 (m, 4H), 3.77 (s, 3H), 3.35-3.39 (m, 4H), 3.18-3.22 (m, 4H),; MS:  $m/z$  360.9 ( $\text{M} + \text{H}$ ) $^+$ .

### Example 16



**Cpd 47: 1-[3-(4-Methoxy-phenoxy)biphenyl-4-yl]-4-methyl-piperazine.** To a stirring solution of **Cpd 46** (0.090 g, 0.25 mmol) and 37% aqueous formaldehyde (0.5 mL) in 0.5 mL of acetonitrile was added sodium cyanoborohydride (0.06 g, 0.9 mmol) and 0.5 mL of acetic acid. The resulting mixture was stirred at 20°C for 3 h, and then was quenched by adding saturated aqueous  $\text{NaHCO}_3$ . Solvent was removed by evaporation and the aqueous residue was extracted with EtOAc. The organic layer was washed successively with 1N aqueous  $\text{NaOH}$ , 1N aqueous  $\text{HCl}$ , and brine, dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The resulting crude residue was purified by reverse phase HPLC to afford **Cpd 47** as a TFA salt.  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.16-7.48 (m, 7H), 7.09 (m, 1H), 6.92 (m, 4H), 3.77 (s, 3H), 3.68-3.72 (m, 2H), 3.52-3.55 (m, 2H), 3.07-3.13 (m, 4H), 2.90 (s, 3H),; MS:  $m/z$  374.9 ( $\text{M} + \text{H}$ ) $^+$ .

## Example 17



**A. 2-(S)-{[4-Cyano-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (17a).** A mixture of Compound **1f** (0.13 g, 0.30 mmol), zinc (II) cyanide (0.036 mmol, 0.30 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.017 g, 0.015 mmol) in 1.2 mL of DMF was irradiated in a microwave reactor at 160°C for 6 min. The residue was purified by preparative TLC, eluting with 1:1 EtOAc:hexanes, to give Compound **17a** (0.080 g, 63% yield). MS: *m/z* 426.2 (M + H)<sup>+</sup>.

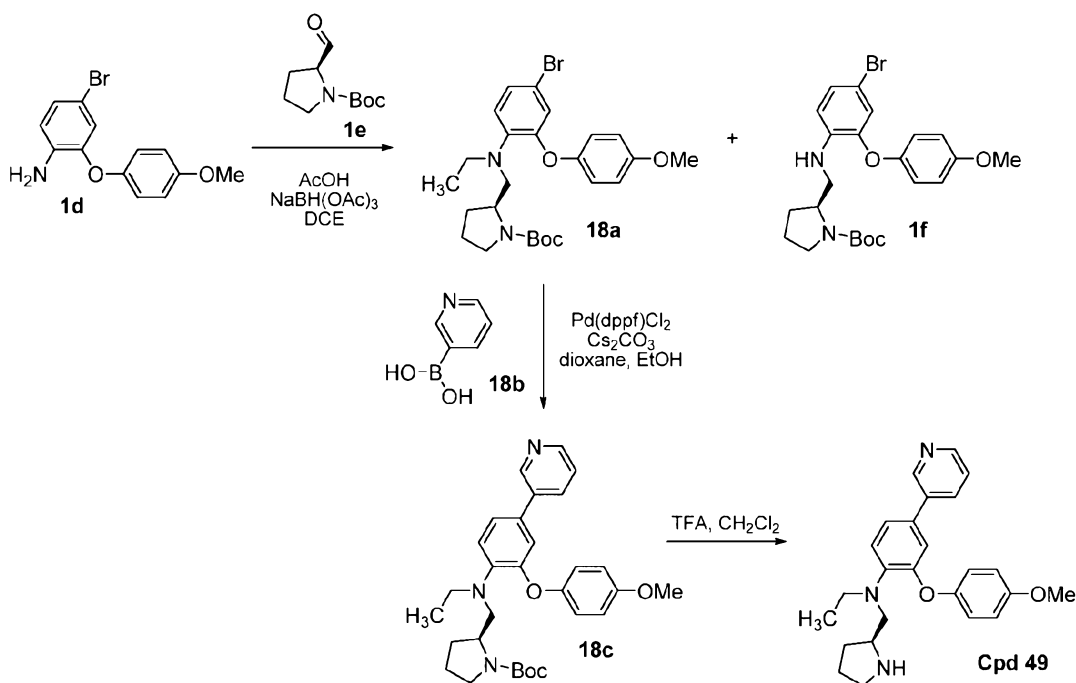
**B. 2-(S)-{[4-(N-Hydroxycarbamimidoyl)-2-(4-methoxy-phenoxy)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (17b).** Hydroxylamine hydrochloride (0.023 g, 0.32 mmol), NaHCO<sub>3</sub> (0.040 g, 0.48 mmol), and 0.2 mL of water were stirred until CO<sub>2</sub> evolution ceased. A suspension of compound **17a** (0.069 g, 0.16 mmol) in 0.5 mL of EtOH was added. The mixture was irradiated in a microwave reactor at 160°C for 16 min. After evaporation of the solvent, the residue was dissolved in EtOAc and purified by preparative TLC, eluting with 1:1 EtOAc:hexanes, to give Compound **17b** (0.038 g, 52% yield). MS: *m/z* 459.3 (M + H)<sup>+</sup>.

**C. 2-(S)-{[2-(4-Methoxy-phenoxy)-4-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-phenylamino]-methyl}-pyrrolidine-1-carboxylic acid tert-butyl ester (17c).** DBU (0.071 g, 0.069 mL, 0.464 mmol) was added to a stirring solution of Compound **17b** (0.053

g, 0.116 mmol) and 1,1'-carbonyldiimidazole (0.021 g, 0.128 mmol) in 1 mL of CH<sub>3</sub>CN. The mixture was stirred under N<sub>2</sub> for 2 days and was then purified by filtration through a solid-phase extraction (SPE) column. Evaporation of the solvent afforded Compound **17c**. MS: *m/z* 483.2 (M + H)<sup>+</sup>.

- 5           **D. Cpd 48: (S)-3-{3-(4-Methoxy-phenoxy)-4-[(pyrrolidin-2-ylmethyl)-amino]-phenyl}-4H-[1,2,4]oxadiazol-5-one.** A mixture of Compound **17c** (0.048 g, 0.099 mmol), TFA, and CH<sub>2</sub>Cl<sub>2</sub> was stirred at 20°C for 4 h. After concentration, the residue was purified by reverse phase HPLC to afford **Cpd 48** as a TFA salt (0.018 g, 30% yield). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.39 (d, 1H), 6.92-7.07 (m, 6H), 3.88-3.98 (m, 1H), 3.80 (s, 3H),  
10   3.53-3.60 (m, 2H) 3.30-3.33 (m, 2H), 2.23-2.31 (m, 1H), 2.05-2.13 (m, 2H), 1.75-1.88 (m, 1H); MS: *m/z* 383.1 (M + H)<sup>+</sup>.

### Example 18



- 15           **A. 2-(S)-({[4-Bromo-2-(4-methoxy-phenoxy)-phenyl]-ethyl-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**18a**).** A mixture of Compound **1d** (11.8 g, 40 mmol) and Compound **1e** in 5 mL of HOAc and 60 mL of 1,2-dichloroethane was

stirred for 1 h at 20°C. NaBH(OAc)<sub>3</sub> was added in portions over a 15 min period, and the mixture was allowed to stir at 20°C for 2 1/2 days. Saturated aqueous K<sub>2</sub>CO<sub>3</sub> (200 mL) was added slowly, followed by CH<sub>2</sub>Cl<sub>2</sub> (500 mL). The organic layer was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 200 mL). The combined organic  
5 fractions were dried over MgSO<sub>4</sub>, treated with charcoal, filtered over Celite, and evaporated to yield 26.9 g of a dark brown oil. The residue was purified via flash column chromatography (SiO<sub>2</sub>), eluting with a hexanes-EtOAc gradient to yield Compound **1f** (6.93 g, 36% yield) and Compound **18a** (6.63 g, 33% yield). MS: *m/z* 505.1/507.1 (M + H)<sup>+</sup>.

10        **B. 2-(S)-({Ethyl-[2-(4-methoxy-phenoxy)-4-pyridin-3-yl-phenyl]-amino}-methyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (**18c**).** A mixture of Compound **18a** (0.51 g, 1 mmol), Compound **18b** (0.307 g, 2.5 mmol), Pd(dppf)Cl<sub>2</sub> (0.183 g, 0.25 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.977 g, 3.0 mmol), 0.5 mL of EtOH, and 2.5 mL of dioxane was irradiated in a microwave reactor at 140°C for 15 min. The reaction mixture was filtered  
15 and the solid was washed with 100 mL of EtOAc. The filtrate was washed with 30 mL of saturated aqueous K<sub>2</sub>CO<sub>3</sub> dried over Na<sub>2</sub>SO<sub>4</sub> and charcoal, and concentrated to afford 0.36 g of crude residue containing Compound **18c**.

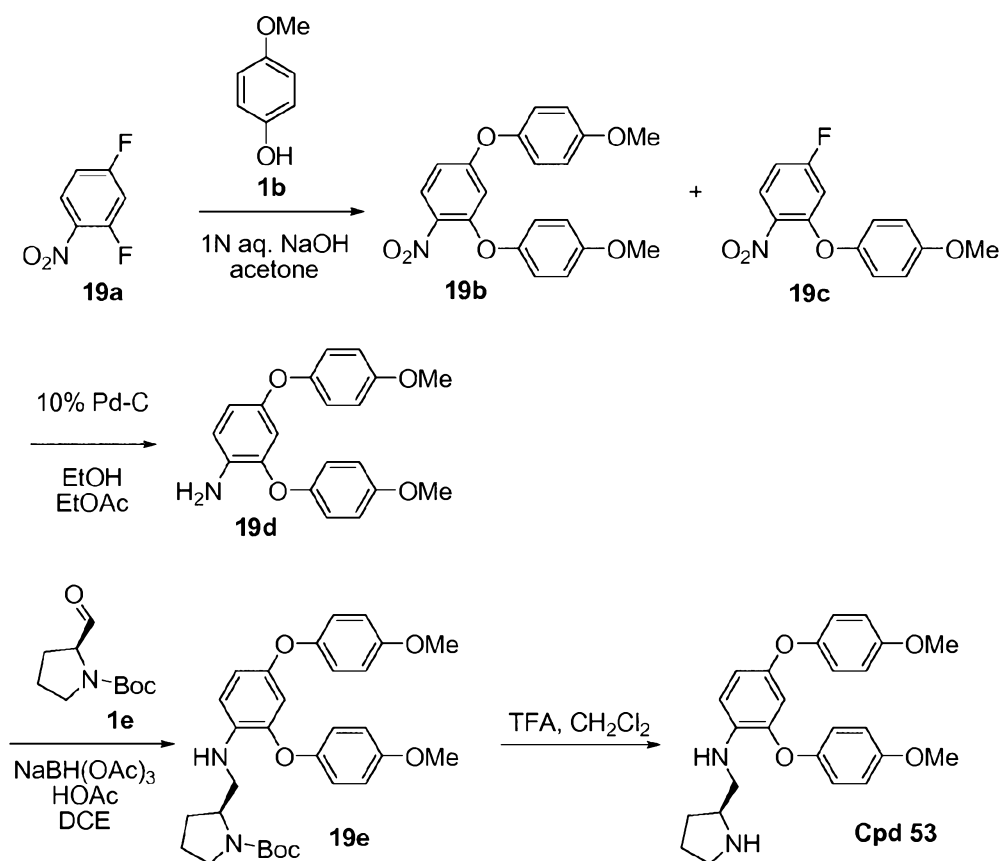
20        **C. Cpd 49: (S)-Ethyl-[2-(4-methoxy-phenoxy)-4-pyridin-3-yl-phenyl]-pyrrolidin-2-ylmethyl-amine.** TFA (5 mL) was added dropwise to a solution of the residue from Step B above in 10 mL of CH<sub>2</sub>Cl<sub>2</sub>. The mixture was stirred for 4 h at 20°C and was then evaporated. The residue was dissolved in 100 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with 20 mL of 1N aqueous NaOH. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by reverse phase HPLC. Fractions containing the  
25 desired product were concentrated, dissolved in 100 mL of CH<sub>2</sub>Cl<sub>2</sub>, and washed with 10 mL of 1N aqueous NaOH. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated, redissolved in CH<sub>2</sub>Cl<sub>2</sub>, treated with 6 mL of 1N HCl in Et<sub>2</sub>O, and evaporated to afford a lightly yellow solid, **Cpd 49**, as an HCl salt (0.130 g, 27% yield for 2 steps). <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): 9.64 (1H, s, broad), 9.20 (1H, d), 8.93, 1H, s, broad), 8.84 (1H, d), 8.78 (1H, d), 8.07 (1H, dd), 7.71 (1H, dd), 7.46 (1H, d), 7.42 (1H, d), 7.00 (4H, m), 3.79

(3H, s), 3.7-3.1 (7H, m), 2.0-1.75 (3H, m), 1.55 (1H, m), 1.02 (3H, t); MS:  $m/z$  404.2 ( $M + H$ )<sup>+</sup>.

Following the procedure described above for Example 18 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compounds of the present invention were prepared:

Cpd	MS ( $M + H$ ) <sup>+</sup>
<b>50</b>	422.2
<b>51</b>	405.1
<b>52</b>	429.1

### Example 19





**A. 2,4-Bis-(4-methoxy-phenoxy)-nitrobenzene (19b).** A solution of 2,4-difluoronitrobenzene (Compound **19a**, 0.5 g, 3.1 mmol) in 15 mL of acetone was added to a mixture of Compound **1b** (0.86 g, 6.9 mmol) and 6.9 mL of 1N aqueous NaOH in 5 mL of acetone. The mixture was heated at 55°C for 3 days and then at 80°C for 5 h. The reaction mixture was concentrated to remove acetone and the residue was loaded onto a 10 mL solid-phase extraction (SPE) column. Elution with CH<sub>2</sub>Cl<sub>2</sub> and concentration of the eluent yielded 1.5 g of a 1:4 mixture of Compound **19c** and Compound **19b** that was used without purification. MS: *m/z* 368 (M + H)<sup>+</sup>.

**B. 2,4-Bis-(4-methoxy-phenoxy)-aniline (19d).** The mixture containing Compounds **19b** and **19c** prepared in Step A were combined with 50 mg of 10% Pd-C in 50 mL of EtOH/EtOAc and stirred at 20°C under a hydrogen atmosphere (14.7 psi) for 17 h. The mixture was filtered through Celite and concentrated. The residue was taken up in MeOH, filtered through a 0.4 µm filter disk, and concentrated to give Compound **19d**. MS: *m/z* 338.1 (M + H)<sup>+</sup>.

**C. (S)-2-[[2,4-Bis-(4-methoxy-phenoxy)-phenylamino]-methyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (19e).** A mixture of Compound **19d** (0.051 g, 0.15 mmol), Compound **1e** (0.033 g, 0.31 mL, 0.17 mmol), HOAc (0.017 mL, 0.3 mmol), and 0.4 mL of DCE was stirred at 20°C for 2.5 h. NaBH(OAc)<sub>3</sub> (0.089 g, 0.42 mmol) was added and the mixture was stirred at 20°C for 20 h. The reaction mixture was purified using a 1 mL SPE column, eluting with CH<sub>2</sub>Cl<sub>2</sub>, to give Compound **19e**.

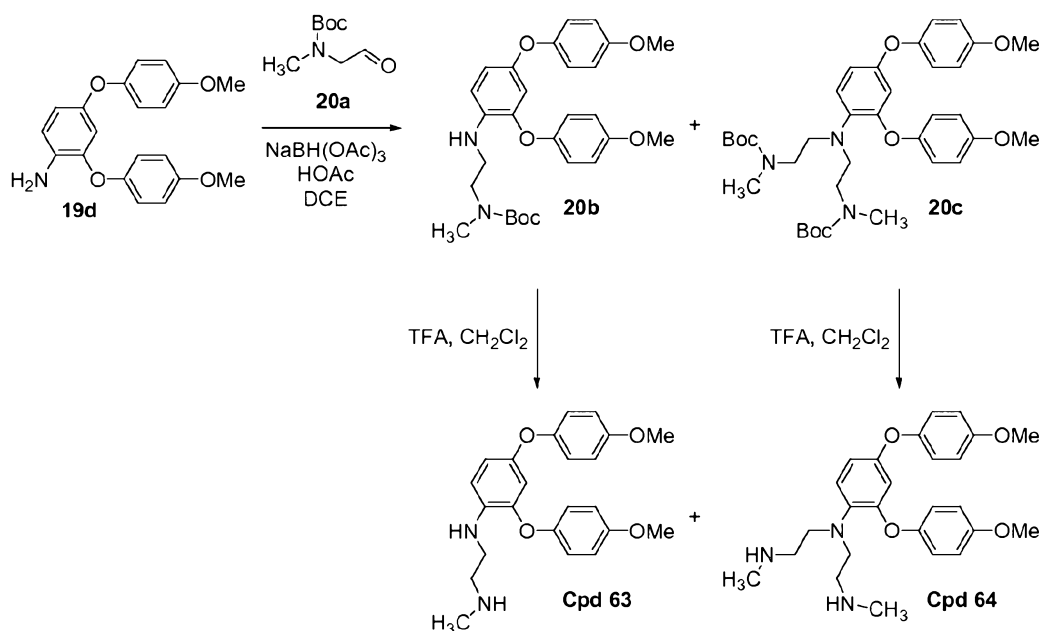
**D. Cpd 53: (S)-[2,4-Bis-(4-methoxy-phenoxy)-phenyl]-pyrrolidin-2-ylmethylamine.** Compound **19e** was dissolved in 50% TFA/CH<sub>2</sub>Cl<sub>2</sub> and stirred at 20°C for 45 min. After concentration, the residue was purified by reverse phase HPLC to afford **Cpd 53** as a TFA salt (0.082 g, 84% yield). MS: *m/z* 421.2 (M + H)<sup>+</sup>.

Following the procedure described above for Example 19 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compounds of the present invention were prepared:

Cpd	MS (M + H) <sup>+</sup>
<b>54</b>	421.1
<b>55</b>	411.1

Cpd	MS (M + H) <sup>+</sup>
<b>56</b>	421.1
<b>57</b>	447.0
<b>60</b>	447.2
<b>61</b>	435.2
<b>62</b>	435.2

### Example 20



- A. {2-[2,4-Bis-(4-methoxy-phenoxy)-phenylamino]-ethyl}-methyl-carbamic acid *tert*-butyl ester (20b); and (2-{[2,4-Bis-(4-methoxy-phenoxy)-phenyl]-[2-(tert-butoxycarbonyl-methyl-amino)-ethyl]-amino}-ethyl)-methyl-carbamic acid *tert*-butyl ester (20c).** HOAc (0.034 mL, 0.59 mmol) and  $\text{NaBH}(\text{OAc})_3$  (0.175 g, 0.83 mmol) were added to a solution of Compound **19d** (0.102 g, 0.30 mmol) and Compound **20a** (0.112 g, 0.32 mL, 0.17 mmol) in DCE and the mixture was stirred at 20°C for 18 h. Water (0.2 mL) was added and the reaction mixture was purified using a 3 mL SPE column, eluting with  $\text{CH}_2\text{Cl}_2$ , to give a mixture of Compound **20b** and Compound **20c**.

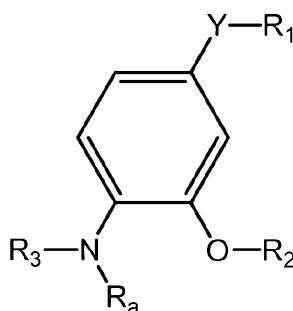
**B. Cpd 63: N-[2,4-Bis-(4-methoxy-phenoxy)-phenyl]-N'-methyl-ethane-1,2-diamine; and Cpd 64: N-[2,4-Bis-(4-methoxy-phenoxy)-phenyl]-N'-methyl-N-(2-methylamino-ethyl)-ethane-1,2-diamine.**

The mixture of Compound **20b** and Compound **20c** prepared in Step A was dissolved in TFA/CH<sub>2</sub>Cl<sub>2</sub> and stirred at 20°C. After concentration, the residue was purified by reverse phase HPLC to afford **Cpd 63** (0.139 g, 62% yield) and **Cpd 64** (0.013 g, 5.6% yield)., each as a TFA salt. **Cpd 63**: MS: *m/z* 395.2 (M + H)<sup>+</sup>. **Cpd 64**: MS: *m/z* 452.3 (M + H)<sup>+</sup>.

Following the procedure described above for Example 20 and substituting the appropriate reagents, starting materials, and purification methods known to those skilled in the art, the following compounds of the present invention were prepared:

Cpd	MS (M + H) <sup>+</sup>
<b>58</b>	407.1
<b>59</b>	476.3

Compounds 1 through 64 of Formula (I) in the table below were synthesized using the procedures described above.



Formula (I)

Table 1.

Cpd No.	R <sub>1</sub>	Y	R <sub>2</sub>	R <sub>3</sub>	R <sub>a</sub>	R <sub>3</sub> -N-R <sub>a</sub>	R <sub>3</sub> stereo chem
<b>1</b>	2-(N,N-diethyl amino carbonyl)	(E)-vinyl-	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S

Cpd No.	R <sub>1</sub>	Y	R <sub>2</sub>	R <sub>3</sub>	R <sub>a</sub>	R <sub>3</sub> -N-R <sub>a</sub>	R <sub>3</sub> stereo chem
2	2-(N,N-diethyl amino carbonyl)	ethyl	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
3	2-(4-methoxy-phenyl)	ethyl	4-methoxy-phenyl	pyrrolidin-2-ylmethyl	H		2S
4	2-(3-methoxy-phenyl)	ethyl	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
5	2-phenyl	ethyl	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
6	2-(4-fluoro-phenyl)	ethyl	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
7	2-(3-fluoro-phenyl)	ethyl	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
8	2-[3-(N,N-diethyl amino carbonyl) phenyl]	ethyl	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
9	N,N-diethyl amino carbonyl	a bond	phenyl	pyrrolidin-2-yl methyl	H		2S
10	N,N-diethyl amino carbonyl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
11	N,N-diethyl amino carbonyl	a bond	2-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
12	phenyl	a bond	4-cyano-phenyl	pyrrolidin-2-yl methyl	H		2S
13	phenyl	a bond	3-cyano-phenyl	pyrrolidin-2-yl methyl	H		2S
14	phenyl	a bond	phenyl	pyrrolidin-2-yl methyl	H		2S
15	phenyl	a bond	3-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
16	phenyl	a bond	4-fluoro-phenyl	pyrrolidin-2-yl methyl	H		2S

Cpd No.	R <sub>1</sub>	Y	R <sub>2</sub>	R <sub>3</sub>	R <sub>a</sub>	R <sub>3</sub> -N-R <sub>a</sub>	R <sub>3</sub> stereo chem
17	phenyl	a bond	4-trifluoromethoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
18	phenyl	a bond	2,6-dichloro-phenyl	pyrrolidin-2-yl methyl	H		2S
19	phenyl	a bond	4-methoxy-phenyl	2-(N-methylamino) ethyl	H		
20	phenyl	a bond	4-methoxy carbonyl-phenyl	pyrrolidin-2-yl methyl	H		2S
21	phenyl	a bond	3-methoxy carbonyl-phenyl	pyrrolidin-2-ylmethyl	H		2S
22	phenyl	a bond	2,4-dichloro-phenyl	pyrrolidin-2-yl methyl	H		2S
23	phenyl	a bond	4-methoxy-phenyl	piperidin-4-yl	H		
24	5-cyano-pyridin-3-yl	a bond	4-methoxy-phenyl	4-fluoro-pyrrolidin-2-yl methyl	H		2S,4R
25	5-fluoro-pyridin-3-yl	a bond	4-methoxy-phenyl	4-fluoro-pyrrolidin-2-yl methyl	H		2S,4R
26	5-methylthio-pyridin-3-yl	a bond	4-methoxy-phenyl	4-fluoro-pyrrolidin-2-yl methyl	H		2S,4R
27	5-methoxy-pyridin-3-yl	a bond	4-methoxy-phenyl	4-fluoro-pyrrolidin-2-yl methyl	H		2S,4R
28	5-methyl-pyridin-3-yl	a bond	4-methoxy-phenyl	4-fluoro-pyrrolidin-2-yl methyl	H		2S,4R
29	phenyl	a bond	4-amino carbonyl-phenyl	pyrrolidin-2-yl methyl	H		2S
30	phenyl	a bond	3-amino carbonyl-phenyl	pyrrolidin-2-yl methyl	H		2S
31	phenyl	a bond	4-carboxy-phenyl	pyrrolidin-2-yl methyl	H		2S
32	phenyl	a bond	3-carboxy-phenyl	pyrrolidin-2-yl methyl	H		2S

Cpd No.	R <sub>1</sub>	Y	R <sub>2</sub>	R <sub>3</sub>	R <sub>a</sub>	R <sub>3</sub> -N-R <sub>a</sub>	R <sub>3</sub> stereo chem
33	phenyl	a bond	4-(N,N-diethylamino carbonyl) phenyl	pyrrolidin-2-yl methyl	H		2S
34	phenyl	a bond	3-(N,N-diethylamino carbonyl) phenyl	pyrrolidin-2-yl methyl	H		2S
35	phenyl	a bond	4-methoxy-phenyl	pyrrolidin-2-ylmethyl	H		2S
36	naphthalen-2-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
37	naphthalen-1-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
38	pyridin-4-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
39	pyridin-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
40	furan-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
41	thiophen-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
42	pyrimidin-5-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
43	5-fluoro-pyridin-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
44	5-cyano-pyridin-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
45	pyridin-3-yl	a bond	4-hydroxy-phenyl	pyrrolidin-2-yl methyl	H		2S
46	phenyl	a bond	4-methoxy-phenyl			piperazin-1-yl	
47	phenyl	a bond	4-methoxy-phenyl			4-methyl-piperazin-1-yl	

Cpd No.	R <sub>1</sub>	Y	R <sub>2</sub>	R <sub>3</sub>	R <sub>a</sub>	R <sub>3</sub> -N-R <sub>a</sub>	R <sub>3</sub> stereo chem
48	5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
49	pyridin-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	ethyl		2S
50	5-fluoro-pyridin-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	ethyl		2S
51	pyrimidin-5-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	ethyl		2S
52	5-cyano-pyridin-3-yl	a bond	4-methoxy-phenyl	pyrrolidin-2-yl methyl	ethyl		2S
53	4-methoxy-phenyl	O	4-methoxy-phenyl	pyrrolidin-2-yl methyl	H		2S
54	4-methoxy-phenyl	O	4-methoxy-phenyl	piperidin-3-yl	H		racemic
55	4-methoxy-phenyl	O	4-methoxy-phenyl	3-hydroxy-2( <i>R</i> )-amino-propyl	H		2R
56	4-methoxy-phenyl	O	4-methoxy-phenyl	piperidin-4-yl	H		
57	4-methoxy-phenyl	O	4-methoxy-phenyl	8-azabicyclo[3.2.1]octan-3-yl	H		mixture of endo / exo isomers
58	4-methoxy-phenyl	O	4-methoxy-phenyl	azetidin-3-yl-methyl	H		
59	4-methoxy-phenyl	O	4-methoxy-phenyl	azetidin-3-yl-methyl	azetidin-3-yl-methyl		
60	4-methoxy-phenyl	O	4-methoxy-phenyl	1-azabicyclo[2.2.2]octan-3-yl	H		mixture of endo / exo isomers
61	4-methoxy-phenyl	O	4-methoxy-phenyl	piperidin-3-yl methyl	H		racemic
62	4-methoxy-phenyl	O	4-methoxy-phenyl	3-amino-cyclohexyl	H		mixture of 4 isomers

Cpd No.	R <sub>1</sub>	Y	R <sub>2</sub>	R <sub>3</sub>	R <sub>a</sub>	R <sub>3</sub> -N-R <sub>a</sub>	R <sub>3</sub> stereo chem
63	4-methoxy-phenyl	O	4-methoxy-phenyl	2-(N-methylamino) ethyl	H		
64	4-methoxy-phenyl	O	4-methoxy-phenyl	2-(N-methylamino) ethyl	2-(N-methyl amino) ethyl		

### Biological Examples

5

#### In Vitro Assays

##### Example 1

#### **NG108-15, 24-Well Delta Opioid Receptor Binding Assay**

Methods: NG108-15 cell membranes were purchased from Applied Cell Sciences (Rockville, MD). 5 mg/mL of membrane protein suspended in 10 mM TRIS-HCl pH 7.2, 2 mM EDTA, 10% sucrose. With several brief pulses from a Polytron homogenizer, each vial was homogenized in 5 mls of 50mM Tris Buffer, pH 7.4. The homogenate was diluted in 50mM Tris Buffer containing 5 mM MgCl<sub>2</sub> to 330ug/ml in the working solution for a final concentration of 133ug/well. This particulate preparation was used for the 24-well delta opioid binding assay.

Following incubation with the delta selective peptide ligand ~0.2 nM [<sup>3</sup>H]naltrindole at 25°C for 2.5 h in a 24-well plate with total volume of 1 mL, the plate contents were filtered through a UniFilter24, GF/B. This plate was presoaked in 0.3%PEI and filtered through a 24-well Harvester. The UniFilter24 was rinsed three times with 2 mL of 10 mM HEPES (pH 7.4), and dried in an oven at 37°C for 1.5 hours. To each well, was added 150 µL of Scint0 (PerkinElmer, Cat#6013611). The plates were then read on a TopCount.



Analysis: The data from the scintillation counter were used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound was evaluated) or a  $K_i$  value (when a range of concentrations was tested). Non-specific binding (N.S.-1mM naloxone) was used as the negative control, while the Total Binding (T.B.-Membrane and ligand only) was used as the positive control. If one concentration was screened, the % inhibition was calculated as (cpms of total binding minus cpms of compound) divided by (cpms of T.B.minus cpms of N.S). The triplicate % Inhibitions were averaged and reported. If multiple concentrations were generated, the values were analyzed using the one-site binding non-linear regression program in Prism to determine  $K_i$  values. The bottom and top values are globally shared. The triplicate  $K_i$  values are then averaged and reported.

The data obtained are shown in Table 2, below.

#### Example 2

##### **Rat Brain Delta Opioid Receptor Binding Assay**

Procedure: Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) were killed by CO<sub>2</sub>, and their brains were 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<sup>®</sup>-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<sub>2</sub> with several brief pulses from a Polytron homogenizer. This particulate preparation was used for the delta opioid binding assays. Following incubation with the delta selective peptide ligand ~4 nM [<sup>3</sup>H]DPDPE or 0.25 nM [<sup>3</sup>H]naltrindole at 25°C for 2.5 h in a 96-well plate with total volume of 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 650 W microwave oven for 1.75 min twice. To each sample area 2 x 50  $\mu$ L of Betaplate Scint scintillation fluid (LKB) was added and the radioactivity was quantified on a LKB (Wallac) 1205 BetaPlate liquid scintillation counter.

Analysis: The data from the scintillation counter were used to calculate either the  
5 % inhibition compared to control binding (when only a single concentration of test compound was evaluated) or a  $K_i$  value (when a range of concentrations was tested). Percent inhibition was calculated as: [(total dpm-test compound dpm)/(total dpm-nonspecific dpm)]\*100.  $K_d$  and  $K_i$  values were calculated using GraphPad PRISM data analysis program. The data obtained are shown in Table 2, below.

10

### Example 3

#### **Rat Brain Mu Opioid Receptor Binding Assay**

Procedure: Male, Wistar rats (150-250 g, VAF, Charles River, Kingston, NY) were killed by CO<sub>2</sub>, and their brains were removed and placed immediately in ice cold Tris HCl  
15 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<sup>®</sup>-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  
20 was resuspended in the same volume of Tris buffer containing 5 mM MgCl<sub>2</sub> with several brief pulses from a Polytron homogenizer. This particulate preparation was used for the mu opioid binding assays. Following incubation with the mu selective peptide ligand, ~0.8 nM [<sup>3</sup>H]DAMGO, at 25°C for 2.5 h in a 96-well plate with total assay volume of 1 mL, the plate contents were filtered through Wallac filtermat B sheets on a Tomtec 96-well  
25 harvester. The filters were rinsed three times with 2 mL of 10 mM HEPES (pH 7.4), and dried in a 650 W microwave oven for 1.75 min twice. To each sample area 2 X 40  $\mu$ L of Betaplate Scint scintillation fluid (LKB) was added and the radioactivity was quantified on a LKB (Wallac) 1205 BetaPlate liquid scintillation counter.

Analysis: The data from the scintillation counter were used to calculate either the % inhibition compared to control binding (when only a single concentration of test compound was evaluated) or a  $K_i$  value (when a range of concentrations was tested). Percent inhibition was calculated as:  $[(\text{total dpm-test compound dpm})/(\text{total dpm-nonspecific dpm})]*100$ .  $K_d$  and  $K_i$  values were calculated using GraphPad PRISM data analysis program. The data obtained are shown in Table 2, below.

Table 2. Delta and Mu Opioid Receptor Binding Data

Cpd No.	$\delta$ -binding NG108 cell membrane $K_i$ ( $\mu\text{M}$ )	$\delta$ -binding (DPDPE ligand) $K_i$ ( $\mu\text{M}$ )	$\delta$ -binding (Naltrindole ligand) $K_i$ ( $\mu\text{M}$ )	$\mu$ -binding $K_i$ ( $\mu\text{M}$ )
1			0.006081	3.3659
2			0.02641	>100
3			0.1197	>10
4			0.21	>10
5			0.2395	>10
6			0.6836	>10
7			0.2288	>10
8			0.1269	9.00119
9			1.023	>10
10			0.9356	0.9356
11		0.1053		>10
12			0.9959	>10
13			0.4018	>10
14			0.1131	>10
15			0.2886	>10
16			0.4191	>10
17			1.472	>10
18			0.1075	>10
19			0.192	>10
20			0.7789	>10
21			0.8869	>10
22			0.6978	>10
23			0.4615	>10
27			1.001	>10

Cpd No.	$\delta$ -binding NG108 cell membrane $K_i$ ( $\mu$ M)	$\delta$ -binding (DPDPE ligand) $K_i$ ( $\mu$ M)	$\delta$ -binding (Naltrindole ligand) $K_i$ ( $\mu$ M)	$\mu$ -binding $K_i$ ( $\mu$ M)
28			0.006814	4.673
29			0.1467	>10
30			0.1265	5.7956
31			7.691	>10
32			2.667	>10
33			0.2843	9.30465
34			0.3095	>10
35		0.02885		>10
36			0.2905	>10
37			0.3009	>10
38			0.0155	4.3621
39	0.001646		0.02213	3.1067
40			0.2051	>10
41			0.2896	>10
42	0.001388			
43	0.00076			
44	0.000436			
45			0.00542	4.4555
46			0.07971	>10
47			2.223	>10
48		0.492		9.705
49	0.02897			
50	0.02303			
51	0.077			
52	0.009328			
53		0.1053		>10
54		0.492		9.705
55		1.367		>10
56		1.729		>10
57		1.43		>10
58		0.7027		>10
59		2.275		>10
60		0.1577		>10
61		0.111		>10
62		0.04088		1.6417
63		0.02374		>10
64		1.536		>10

#### Example 4

#### **[<sup>35</sup>S]GTPγS Binding Assay in NG108-15 Cell Membranes (delta opioid functional assay)-200nM Screen**

5           Methods: NG108-15 cell membranes were purchased from Applied Cell Sciences (Rockville, MD). 5 mg/mL of membrane protein suspended in 10 mM TRIS-HCl pH 7.2, 2 mM EDTA, 10% sucrose. Membranes were maintained at 4-8°C. A 1 mL volume of membranes was added into 10 mL cold binding assay buffer. The assay buffer contained 50 mM Tris, pH 7.6, 5 mM MgCl<sub>2</sub>, 100 mM NaCl, 1 mM DTT and 1 mM EGTA. The  
10   membrane suspension was homogenized twice with a Polytron, and centrifuged at 3000 rpm for 10 min. The supernatant was then centrifuged at 18,000 rpm for 20 min. Ten mL assay buffer was added into the pellet containing tube. The pellet and buffer were mixed with a Polytron.

          Incubation procedure: The pellet membranes (75 μg/mL) were preincubated with  
15   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 [<sup>35</sup>S] GTPγS in the same Tris buffer containing 100 μM GDP in total volume of 200 μL. 200nM of receptor agonists was used to stimulate [<sup>35</sup>S]- GTPγS binding. The basal binding was tested in the absence of agonists and non-specific binding was tested in the presence of 10 μM  
20   unlabeled GTPγS. The data were analyzed on a Packard Top Count and are shown in Table 3, below.

#### DATA

% of Basal = (stimulated - non specific)\*100/(basal - non specific).

Relative Efficacy of a compound at 200nM

25   =(% of Basal of test compound at 200nM)/(Calculated Max of SNC80 dose response. Curve in prism).

### Example 5

#### [<sup>35</sup>S]GTPγS Binding Assays in CHO-hMOR Cell Membranes (mu opioid functional assay)

5           Methods: 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. A 1mL volume of membranes was added to 15 mL cold binding assay buffer containing 50 mM HEPES, pH 7.6, 5 mM MgCl<sub>2</sub>, 100 mM NaCl, 1 mM DTT and 1 mM EDTA. The  
10   membrane suspension was homogenized with a Polytron and centrifuged at 3,000 rpm for 10 min. The supernatant can then be centrifuged at 18,000 rpm for 20 min. The pellet was resuspended in 10 mL assay buffer with a Polytron. The membranes were preincubated with wheat germ agglutinin coated SPA beads (Amersham) at 25 ° C for 45 min in the assay buffer. The SPA bead (5 mg/mL) coupled membranes (10 μg/mL) were then  
15   incubated with 0.5 nM [<sup>35</sup>S]GTPγS in the assay buffer. The basal binding was that taking place in the absence of added test compound; this unmodulated binding was considered as 100%, with agonist stimulated binding rising to levels significantly above this value. A range of concentrations of receptor agonist was used to stimulate [<sup>35</sup>S]GTPγS binding. Both basal and non-specific binding were tested in the absence of agonist; non-specific  
20   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:

25                           % stimulation =  $\frac{(\text{test compound cpm} - \text{non-specific cpm})}{(\text{basal cpm} - \text{non-specific cpm})} \times 100$

$$\% \text{ inhibition} = \frac{(\% \text{ stimulation by } 1 \mu\text{M DAMGO} - \% \text{ stimulation by test compound})}{(\% \text{ stimulation by } 1 \mu\text{M DAMGO} - 100)} \times 100$$

EC<sub>50</sub> values were calculated using GraphPad Prism and are shown in Table 3, below.

5

Table 3. Delta Opioid Receptor Functional Data

Cpd No.	GTPγS δ-RelEfficacy @200 nM	GTPγS δ-opioid receptor EC <sub>50</sub> (μM)	GTPγS δ-opioid receptor Rel Efficacy	GTPγS δ-opioid receptor %Inh @10 μM
<b>1</b>		0.1093	0.8328	2.2554
<b>2</b>		0.0391	0.8333	22.78
<b>11</b>		0.3194		
<b>18</b>		1.0428	0.763	23.395
<b>24</b>	1.01	0.0461	1.0158	
<b>25</b>	0.78	0.0924	1.0217	
<b>26</b>	0.7	0.1873	1.0716	
<b>28</b>		0.1651	0.8756	
<b>30</b>		1.0245	0.2668	36.491

Cpd No.	GTP $\gamma$ S $\delta$ -RelEfficacy @200 nM	GTP $\gamma$ S $\delta$ -opioid receptor EC <sub>50</sub> ( $\mu$ M)	GTP $\gamma$ S $\delta$ -opioid receptor Rel Efficacy	GTP $\gamma$ S $\delta$ -opioid receptor %Inh @10 $\mu$ M
<b>35</b>		1.4612		1
<b>38</b>		0.4782	0.8323	16.36
<b>39</b>		0.1114	0.9245	13.425
<b>42</b>	0.39			
<b>43</b>	0.43	0.218	1.0908	
<b>44</b>	0.45	0.1176	1.1554	
<b>45</b>		0.0408	0.627	35.642
<b>53</b>		0.3194		28.165
<b>61</b>		4.0729		16.134
<b>62</b>		0.3811		1.733
<b>63</b>		3.1067		25.97

*In Vivo Assay*Example 6

## Mouse Graded Abdominal Irritant Test (GrAIT)



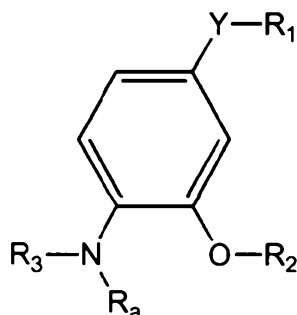
Test compound or vehicle was administered s.c. or p.o. to mice. Following the pretreatment time, an i.p. injection of 0.6 % of acetic acid in 0.5 mL was administered. Five min after acetic acid administration, mice were placed into clear chambers and were continuously observed for 5 min. Behavioral responses including twisting and elongation of the body that extended through the hindlimbs were counted and averaged for the group of animals over the observation period. The results are shown in Table 4 below.

Table 4.

Cpd	dose (mg/kg)	vehicle	route of admin.	no. of animals	pretreatment (min)	# abdominal stretches (vehicle)	# abdominal stretches (cpd)
<b>1</b>	30	10% Solutol	s.c.	5	30	14.1	10.9
<b>10</b>	30	10% Solutol	s.c.	10	30	16.7	11
<b>10</b>	30	10% Solutol	p.o.	5	30	19.8	19
<b>10</b>	100	10% Solutol	p.o.	10	30	19.8	17.9
<b>10</b>	300	10% Solutol	p.o.	5	30	19.8	21.2

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A compound of Formula I



Formula I

wherein

R<sub>1</sub> is selected from the group consisting of

- ix) phenyl optionally substituted with one to two substituents  
independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, hydroxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, chloro, and fluoro; such that only one di(C<sub>1-4</sub>alkyl)aminocarbonyl is present;
  - x) naphthyl;
  - xi) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, hydroxy, fluoro, chloro, and cyano;
  - xii) pyrimidin-5-yl;
  - xiii) furanyl;
  - xiv) thienyl;
  - xv) 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl; and
  - xvi) di(C<sub>1-2</sub>alkyl)aminocarbonyl;
- with the proviso that when R<sub>1</sub> is 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, Y is a bond;
- Y is ethyl, vinyl, or a bond;
- or, Y is O when R<sub>1</sub> is an optionally substituted phenyl;

R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoro, chloro, cyano, trifluoromethoxy, and hydroxy;

or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl, di(C<sub>1-</sub>

5                   4alkyl)aminocarbonyl, C<sub>1-4</sub>alkoxycarbonyl, or carboxy substituent;

R<sub>3</sub> is selected from the group consisting of

xii) 3-amino-cyclohexyl;

xiii) 4-amino-cyclohexyl;

xiv) piperidin-3-yl;

10           xv) piperidin-4-yl;

xvi) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one to two fluoro substituents;

xvii) azetidin-3-ylmethyl;

xviii) 2-(N-methylamino)ethyl;

15           xix) 3-hydroxy-2-amino-propyl;

xx) piperidin-3-ylmethyl;

xxi) 1-azabicyclo[2.2.2]octan-3-yl; and

xxii) 8-azabicyclo[3.2.1]octan-3-yl;

20           or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl optionally substituted with 4-C<sub>1-4</sub>alkyl;

R<sub>a</sub> is hydrogen, 2-(N-methylamino)ethyl, or C<sub>1-2</sub>alkyl optionally substituted with azetidin-3-yl;

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

2. A compound according to claim 1, wherein R<sub>1</sub> is selected from the group consisting of

30           i) phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, and fluoro; such that only one di(C<sub>1-4</sub>alkyl)aminocarbonyl is present;

ii) naphthyl;

- 5  
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- iii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
  - iv) pyrimidin-5-yl;
  - v) furanyl;
  - vi) thienyl; and
  - vii) di(C<sub>1-2</sub>alkyl)aminocarbonyl.
3. A compound according to claim 2, wherein R<sub>1</sub> is selected from the group consisting of
- i) phenyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, and fluoro;
  - ii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
  - iii) pyrimidin-5-yl; and
  - iv) di(C<sub>1-2</sub>alkyl)aminocarbonyl.
4. A compound according to claim 3, wherein R<sub>1</sub> is selected from the group consisting of
- i) phenyl optionally substituted with one methoxy substituent;
  - ii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
  - iii) pyrimidin-5-yl; and
  - iv) di(C<sub>1-2</sub>alkyl)aminocarbonyl.
5. A compound according to claim 1, wherein Y is vinyl or a bond; or, Y is O when R<sub>1</sub> is an optionally substituted phenyl.
6. A compound according to claim 5, wherein Y is vinyl or a bond.

7. A compound according to claim 1, wherein  $R_2$  is phenyl optionally substituted with one to two substituents independently selected from the group consisting of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, fluoro, chloro, and hydroxy; or,  $R_2$  is phenyl substituted with one aminocarbonyl or di( $C_{1-4}$ alkyl)aminocarbonyl substituent.
8. A compound according to claim 7, wherein  $R_2$  is phenyl optionally substituted with one to two substituents independently selected from the group consisting of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, and hydroxy; or,  $R_2$  is phenyl substituted with one aminocarbonyl or di( $C_{1-4}$ alkyl)aminocarbonyl substituent.
9. A compound according to claim 8, wherein  $R_2$  is phenyl optionally substituted with one substituent independently selected from the group consisting of methoxy, hydroxy, aminocarbonyl, and  $C_{1-4}$ alkylcarbonylamino.
10. A compound according to claim 1, wherein  $R_3$  is selected from the group consisting of
- i) 3-amino-cyclohexyl;
  - ii) 4-amino-cyclohexyl;
  - iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one to two fluoro substituents;
  - iv) 2-(N-methylamino)ethyl;
  - v) piperidin-3-ylmethyl; and
  - vi) 1-azabicyclo[2.2.2]octan-3-yl;
- or,  $R_3$  is taken with  $R_a$  and the nitrogen atom to which they are both attached to form piperazinyl.
11. A compound according to claim 10, wherein  $R_3$  is selected from the group consisting of
- i) 3-amino-cyclohexyl;
  - ii) 4-amino-cyclohexyl; and

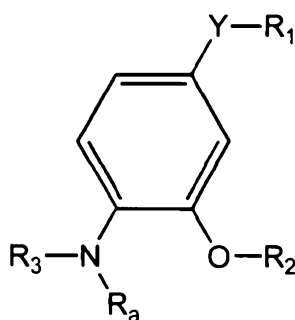
- iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one fluoro substituent;  
or,  $R_3$  is taken with  $R_a$  and the nitrogen atom to which they are both attached to form piperazinyl.

5

12. A compound according to claim 1, wherein  $R_a$  is hydrogen or  $C_{1-2}$ alkyl.

13. A compound according to claim 12, wherein  $R_a$  is hydrogen.

10 14. A compound of Formula (I)



Formula (I)

wherein

$R_1$  is selected from the group consisting of

- 15 viii) phenyl optionally substituted with one to two substituents independently selected from the group consisting of  $C_{1-4}$ alkoxy, di( $C_{1-4}$ alkyl)aminocarbonyl, and fluoro; such that only one di( $C_{1-4}$ alkyl)aminocarbonyl is present;
- ix) naphthyl;
- 20 x) pyridinyl optionally substituted with one substituent selected from the group consisting of  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylthio, fluoro, and cyano;
- xi) pyrimidin-5-yl;
- xii) furanyl;
- 25 xiii) thienyl; and
- xiv) di( $C_{1-2}$ alkyl)aminocarbonyl;

Y is vinyl or a bond; or, Y is O when R<sub>1</sub> is an optionally substituted phenyl;

R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, fluoro, chloro, and hydroxy;

or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl or di(C<sub>1-4</sub>alkyl)aminocarbonyl substituent;

R<sub>3</sub> is selected from the group consisting of

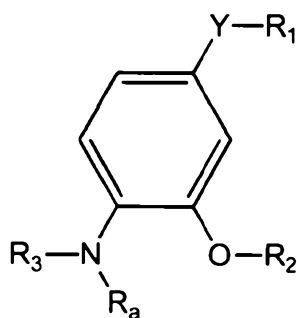
- j) 3-amino-cyclohexyl;
- ii) 4-amino-cyclohexyl;
- iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at the 3- or 4- position with one to two fluoro substituents; 2-(N-methylamino)ethyl; piperidin-3-ylmethyl; and
- v) 1-azabicyclo[2.2.2]octan-3-yl;

or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl;

R<sub>a</sub> is hydrogen or C<sub>1-2</sub>alkyl;

and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

15. A compound of Formula (I)



Formula (I)

wherein

R<sub>1</sub> is selected from the group consisting of

- v) phenyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkoxy, di(C<sub>1-4</sub>alkyl)aminocarbonyl, and fluoro;

- 5
- vii) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
  - viii) pyrimidin-5-yl; and
  - ix) di(C<sub>1-2</sub>alkyl)aminocarbonyl;

Y is vinyl or a bond;

- 10
- R<sub>2</sub> is phenyl optionally substituted with one to two substituents independently selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, and hydroxy;

or, R<sub>2</sub> is phenyl substituted with one aminocarbonyl or di(C<sub>1-4</sub>alkyl)aminocarbonyl substituent;

- 15
- R<sub>3</sub> is selected from the group consisting of

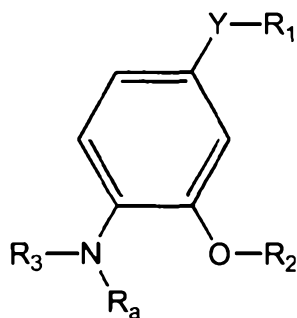
- 20
- j) 3-amino-cyclohexyl;
  - vi) 4-amino-cyclohexyl;
  - vii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at a carbon atom with one to two fluoro substituents;
  - viii) 2-(N-methylamino)ethyl;
  - x) piperidin-3-ylmethyl; and
  - xi) 1-azabicyclo[2.2.2]octan-3-yl;

or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl;

- 25
- R<sub>a</sub> is hydrogen;  
and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

16. A compound of Formula (I)





Formula (I)

wherein

R<sub>1</sub> is selected from the group consisting of

- 5 v) phenyl optionally substituted with one methoxy substituent;
- vi) pyridinyl optionally substituted with one substituent selected from the group consisting of C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkylthio, fluoro, and cyano;
- vii) pyrimidin-5-yl; and
- 10 viii) di(C<sub>1-2</sub>alkyl)aminocarbonyl;

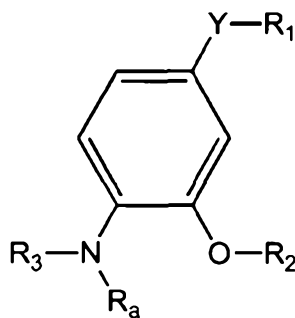
Y is vinyl or a bond;

- 15 R<sub>2</sub> is phenyl optionally substituted with one substituent independently selected from the group consisting of methoxy, hydroxy, aminocarbonyl, and C<sub>1-4</sub>alkylcarbonylamino;

R<sub>3</sub> is selected from the group consisting of

- 20 j) 3-amino-cyclohexyl;
  - ii) 4-amino-cyclohexyl;
  - iii) pyrrolidin-2-ylmethyl wherein pyrrolidin-2-yl is optionally substituted at a carbon atom with one fluoro substituent; and
- or, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazinyl;
- 25 R<sub>a</sub> is hydrogen;
- and enantiomers, diastereomers, and pharmaceutically acceptable salts thereof.

17. A compound of Formula (I)



Formula (I)

selected from the group consisting of

- 5 a compound wherein  $R_1$  is 2-(*N,N*-diethylaminocarbonyl),  $Y$  is (*E*)-vinyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is 2-(*N,N*-diethylaminocarbonyl),  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 10 a compound wherein  $R_1$  is 2-(4-methoxy-phenyl),  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is 2-(3-methoxy-phenyl),  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is 2-phenyl,  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 15 a compound wherein  $R_1$  is 2-(4-fluoro-phenyl),  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is 2-(3-fluoro-phenyl),  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 20 a compound wherein  $R_1$  is 2-[3-(*N,N*-diethylaminocarbonyl)phenyl],  $Y$  is ethyl,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is *N,N*-diethylaminocarbonyl,  $Y$  is a bond,  $R_2$  is phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- 25 a compound wherein  $R_1$  is *N,N*-diethylaminocarbonyl,  $Y$  is a bond,  $R_2$  is 4-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)
- a compound wherein  $R_1$  is *N,N*-diethylaminocarbonyl,  $Y$  is a bond,  $R_2$  is 2-methoxy-phenyl,  $R_3$  is pyrrolidin-2-ylmethyl, and  $R_a$  is H; (2*S*)

- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-cyano-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-cyano-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 5 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-fluoro-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 10 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-trifluoromethoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 2,6-dichloro-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 15 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 2-(*N*-methylamino)ethyl, and R<sub>a</sub> is H;
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxycarbonyl-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-methoxycarbonyl-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 20 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 2,4-dichloro-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-4-yl, and R<sub>a</sub> is H;
- 25 a compound wherein R<sub>1</sub> is 5-cyano-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)
- a compound wherein R<sub>1</sub> is 5-fluoro-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)
- a compound wherein R<sub>1</sub> is 5-methylthio-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)
- 30 a compound wherein R<sub>1</sub> is 5-methoxy-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)

- a compound wherein R<sub>1</sub> is 5-methyl-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 4-fluoro-pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*,4*R*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-aminocarbonyl-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 5 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-aminocarbonyl-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-carboxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-carboxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 10 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-(N,N-diethylaminocarbonyl)phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 3-(N,N-diethylaminocarbonyl)phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 15 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is naphthalen-2-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 20 a compound wherein R<sub>1</sub> is naphthalen-1-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is pyridin-4-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 25 a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is furan-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is thiophen-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 30 a compound wherein R<sub>1</sub> is pyrimidin-5-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)

- a compound wherein R<sub>1</sub> is 5-fluoro-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is 5-cyano-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 5 a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-hydroxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form piperazin-1-yl;
- 10 a compound wherein R<sub>1</sub> is phenyl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is taken with R<sub>a</sub> and the nitrogen atom to which they are both attached to form 4-methyl-piperazin-1-yl;
- a compound wherein R<sub>1</sub> is 5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 15 a compound wherein R<sub>1</sub> is pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- a compound wherein R<sub>1</sub> is 5-fluoro-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- 20 a compound wherein R<sub>1</sub> is pyrimidin-5-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- a compound wherein R<sub>1</sub> is 5-cyano-pyridin-3-yl, Y is a bond, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is ethyl; (2*S*)
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is pyrrolidin-2-ylmethyl, and R<sub>a</sub> is H; (2*S*)
- 25 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-3-yl, and R<sub>a</sub> is H; racemic;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 3-hydroxy-2(*R*)-amino-propyl, and R<sub>a</sub> is H;
- 30 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-4-yl, and R<sub>a</sub> is H;

- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 8-azabicyclo[3.2.1]octan-3-yl, and R<sub>a</sub> is H; mixture of endo / exo isomers;
- 5 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is azetidin-3-yl-methyl, and R<sub>a</sub> is H;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is azetidin-3-yl-methyl, and R<sub>a</sub> is azetidin-3-yl-methyl;
- 10 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 1-azabicyclo[2.2.2]octan-3-yl, and R<sub>a</sub> is H; mixture of endo / exo isomers;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is piperidin-3-ylmethyl, and R<sub>a</sub> is H; racemic;
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 3-amino-cyclohexyl, and R<sub>a</sub> is H; mixture of 4 isomers;
- 15 a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 2-(N-methylamino)ethyl, and R<sub>a</sub> is H; and
- a compound wherein R<sub>1</sub> is 4-methoxy-phenyl, Y is O, R<sub>2</sub> is 4-methoxy-phenyl, R<sub>3</sub> is 2-(N-methylamino)ethyl, and R<sub>a</sub> is 2-(N-methylamino)ethyl;
- 20 and pharmaceutically acceptable salts thereof.
18. A pharmaceutical composition comprising a compound as defined according to claim 1 and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable excipient, and a pharmaceutically acceptable diluent.
- 25 19. A pharmaceutical composition according to claim 18, wherein the composition is a solid, oral dosage form.
20. A pharmaceutical composition according to claim 18, wherein the composition is a syrup, an elixir, or a suspension.
- 30

21. A method for treating mild to severe pain in a subject in need thereof, said method comprising administering to the subject a therapeutically effective amount of a compound as defined according to claim 1.
- 5 22. A method according to claim 21, wherein the mild to severe pain is due to a disease or condition selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, migraine, headache, toothache, burn, sunburn, snake bite, spider bite, insect sting, neurogenic bladder, benign prostatic hypertrophy, interstitial cystitis, rhinitis, contact  
10 dermatitis/hypersensitivity, itch, eczema, pharyngitis, mucositis, enteritis, cellulitis, causalgia, sciatic neuritis, mandibular joint neuralgia, peripheral neuritis, polyneuritis, stump pain, phantom limb pain, post-operative ileus, cholecystitis, postmastectomy pain syndrome, oral neuropathic pain, Charcot's pain, reflex sympathetic dystrophy, Guillain-Barre syndrome, meralgia  
15 paresthetica, burning-mouth syndrome, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, migrainous neuralgia,  
20 idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia, vidian neuralgia, inflammatory bowel disease, irritable bowel syndrome, sinus headache, tension headache, labor, childbirth, menstrual cramps, and cancer.
- 25 23. A method according to claim 21, wherein the pain is selected from the group consisting of inflammatory pain, centrally mediated pain, peripherally mediated pain, visceral pain, structural related pain, cancer pain, soft tissue injury related pain, progressive disease related pain, neuropathic pain and acute  
30 pain from acute injury, acute pain from trauma, acute pain from surgery, chronic pain from headache, chronic pain from neuropathic conditions, chronic pain from post-stroke conditions and chronic pain from migraine.

24. A method for treating or preventing a disease or condition selected from the group consisting of depression, Parkinson's disease, drug abuse, alcohol abuse, gastritis, urinary incontinence, premature ejaculation, diarrhea, cardiovascular disease, and respiratory diseases, said method comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, or salt as defined according to claim 1.
25. Use of a compound as defined according to claim 1 in the manufacture of a medicament for treating mild to severe pain in a subject.
26. Use according to claim 25, wherein the mild to severe pain is due to a disease or condition selected from the group consisting of osteoarthritis, rheumatoid arthritis, fibromyalgia, migraine, headache, toothache, burn, sunburn, snake bite, spider bite, insect sting, neurogenic bladder, benign prostatic hypertrophy, interstitial cystitis, rhinitis, contact dermatitis/hypersensitivity, itch, eczema, pharyngitis, mucositis, enteritis, cellulitis, causalgia, sciatic neuritis, mandibular joint neuralgia, peripheral neuritis, polyneuritis, stump pain, phantom limb pain, post-operative ileus, cholecystitis, postmastectomy pain syndrome, oral neuropathic pain, Charcot's pain, reflex sympathetic dystrophy, Guillain-Barre syndrome, meralgia paresthetica, burning-mouth syndrome, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, migrainous neuralgia, idiopathic neuralgia, intercostals neuralgia, mammary neuralgia, Morton's neuralgia, nasociliary neuralgia, occipital neuralgia, red neuralgia, Sluder's neuralgia, splenopalatine neuralgia, supraorbital neuralgia, vidian neuralgia, inflammatory bowel disease, irritable bowel syndrome, sinus headache, tension headache, labor, childbirth, menstrual cramps, and cancer.
27. Use according to claim 25, wherein the pain is selected from the group consisting of inflammatory pain, centrally mediated pain, peripherally



5 mediated pain, visceral pain, structural related pain, cancer pain, soft tissue injury related pain, progressive disease related pain, neuropathic pain and acute pain from acute injury, acute pain from trauma, acute pain from surgery, chronic pain from headache, chronic pain from neuropathic conditions, chronic pain from post-stroke conditions and chronic pain from migraine.

10 28. Use of a compound, or salt as defined according to claim 1 in the manufacture of a medicament for treating or preventing a disease or condition selected from the group consisting of depression, Parkinson's disease, drug abuse, alcohol abuse, gastritis, urinary incontinence, premature ejaculation, diarrhea, cardiovascular disease, and respiratory diseases, in a mammal.

15 Dated this 27th day of March 2013

Shelston IP

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