TITLE OF THE INVENTION

TRICYCLIC δ– OPIOID MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This Application claims priority to United States Provisional Patent Application No. 60/599,131, filed August 5, 2004, which is hereby incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

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

BACKGROUND OF THE INVENTION

The term "opiate" has been used to designate pharmacologically active 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, 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 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 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 Ca^{2+} channels (Evans, C. J., In: Biological Basis of Substance Abuse, S. G. Korenman & J. D. Barchas, eds., Oxford University Press (1993); 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.

D. Delorme, E. Roberts and Z. Wei, World Patent WO/28275 (1998) discloses diaryl methylidenylpiperidines that are opioid analgesics, but does not disclose or suggest the compounds of the present invention.

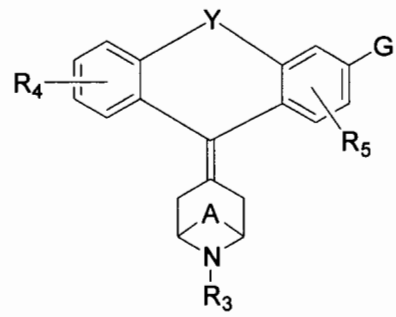
C. Kaiser, and others (J. Med. Chem. 1974, Volume 17, pages 57-61) disclose some piperidylidene derivatives of thioxanthenes, xanthenes, dibenoxepins and acridans that are neuroleptic agents. These authors, however, do not disclose or suggest either the structure or the activity of the compounds of the present invention.

British Patent GB 1128734 (1966) discloses derivatives of 6,11-dihydrodibenzo[b,e]oxepine that are anticholinergic, anti-convulsive, muscle-relaxing, sedating, diuretic, and/or vasoactive agents. These, agents, however, differ significantly from the compounds of the present invention both structurally and pharmacologically.

There is a continuing need for new delta opioid receptor modulators as analgesics. There is a further need for delta opioid receptor selective agonists as analgesics having reduced side effects. There is also a need for delta opioid receptor antagonists as immunosuppressants, antiinflammatory agents, agents for the treatment 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 reduced side effects.

SUMMARY OF THE INVENTION

The present invention is directed to compositions comprising a compound of Formula (I):



Formula (I)

wherein:

G is $-C(Z)NR_1R_2$, C_{6-10}aryl, C_{6-10}arylthio, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, indazolyl, indolyl, indolinyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, and pyridinyl; wherein the C_{6-10}aryl group in the C_{6-10}aryl-containing substituents of G, and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, nitro, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, C_{1-8}alkanylsulfonylamino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

R_1 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, and C_{2-8}alkynyl;

R_2 is a substituent selected from the group consisting of hydrogen; C_{1-8}alkanyl; C_{2-8}alkenyl; C_{2-8}alkynyl; C_{6-10}aryl; and

C_{3-8}cycloalkanyl; provided that when Z is O or S, R_2 is other than hydrogen or unsubstituted C_{1-8}alkanyl; and, wherein C_{1-8}alkanyl of R_2 is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanyloxy, C_{1-6}alkanylthio, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, C_{1-6}alkanyloxycarbonyl, and aryloxy; wherein the phenyl and aryloxy substituents of C_{1-8}alkanyl are optionally further substituted with, and the C_{6-10}aryl and C_{3-8}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, trifluoromethyl, trifluoromethoxy, phenyl, halogen, cyano, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with one to three C_{1-4}alkanyl or C_{1-4}alkanyloxy substituents) and one to two additional substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

or, R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

R_3 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, halo$_{1-3}$(C_{1-8})alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkanyl, cycloalkanyl(C_{1-8})alkanyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, C_{1-8}alkanyloxycarbonyl,

halo$_{1-3}$(C_{1-8})alkanylcarbonyl, formyl, thioformyl, carbamimidoyl, phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, phenyl(C_{1-8})alkenyl, phenyl(C_{1-8})alkynyl, naphthyl(C_{1-8})alkanyl and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiazolyl; wherein phenyl, naphthyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl, thioureido, and fluoro(C_{1-6})alkanyloxy; alternatively, when phenyl and heteroaryl are optionally substituted with alkanyl or alkanyloxy substituents attached to adjacent carbon atoms, the two substituents can together form a fused cyclic alkanyl or cycloheteroalkanyl selected from the group consisting of -$(CH_2)_{3-5}$- , -O$(CH_2)_{2-4}$- , -$(CH_2)_{2-4}$O -, and -O$(CH_2)_{1-3}$O-;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl(C_{2-6})alkynyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, aminocarbonyl, C_{1-6}alkanylaminocarbonyl, di(C_{1-6}alkanyl)aminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, mercapto, aminothiocarbonyl, amidino, hydroxyamidino, phenylcarbonyl, -C(=NOH)phenyl, aminomethyl, hydroxymethyl, methanesulfonylamino, C_{6-10}arylamino (wherein C_{6-10}aryl is optionally substituted with one to three substitutents

independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkoxy, halogen, and hydroxy), dihydroimidazolyl, formylamino, thioformylamino, pyridinylamino, cyano, hydroxycarbonyl, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, thienyl, fluoroalkanyl and fluoroalkanyloxy; or optionally, when R_4 is two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the fused moiety is selected from the group consisting of $-(CH_2)_{3-5}-$, $-O(CH_2)_{2-4}-$, $-(CH_2)_{2-4}O-$, $-O(CH_2)_{1-3}O-$ and $-S-C(NH_2)=N-$;

R_5 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl and fluoro(C_{1-6})alkanyloxy;

A is absent or $-(CH_2)_m-$, wherein m is 2 or 3;

Y is $-(CH_2)_nX-$ or $-X(CH_2)_n-$;

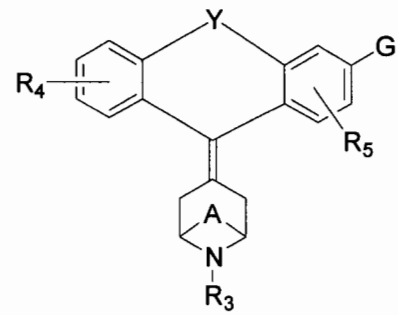
X is O or S

n is 0 or 1;

Z is O, S, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl);

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

The present invention is also directed to compositions comprising a compound of Formula (Ib):



Formula (Ib)

wherein:

G is bromo, chloro, cyano, trifluoromethanesulfonyloxy, C_{1-8}alkanyloxycarbonyl, carboxy, $-C(Z)NR_1R_2$, C_{6-10}aryl, C_{6-10}arylthio, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, indazolyl, indolyl, indolinyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, and pyridinyl; wherein the C_{6-10}aryl group in the C_{6-10}aryl-containing substituents of G and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, nitro, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, C_{1-8}alkanylsulfonylamino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

R_1 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, and C_{2-8}alkynyl;

R_2 is a substituent selected from the group consisting of hydrogen; C_{1-8}alkanyl; C_{2-8}alkenyl; C_{2-8}alkynyl; C_{6-10}aryl; and C_{3-8}cycloalkanyl; provided that when Z is O or S, R_2 is other than

hydrogen or unsubstituted C_{1-8}alkanyl; and, wherein C_{1-8}alkanyl of R_2 is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanyloxy, C_{1-6}alkanylthio, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, C_{1-6}alkanyloxycarbonyl, and aryloxy; wherein the phenyl and aryloxy substituents of C_{1-8}alkanyl are optionally further substituted with, and the C_{6-10}aryl and C_{3-8}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, trifluoromethyl, trifluoromethoxy, phenyl, halogen, cyano, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with one to three C_{1-4}alkanyl or C_{1-4}alkanyloxy substituents) and one to two additional substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

or, R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

R_3 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, halo$_{1-3}$(C_{1-8})alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkanyl, cycloalkanyl(C_{1-8})alkanyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, C_{1-8}alkanyloxycarbonyl, halo$_{1-3}$(C_{1-8})alkanylcarbonyl, formyl, thioformyl, carbamimidoyl,

phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, phenyl(C_{1-8})alkenyl, phenyl(C_{1-8})alkynyl, naphthyl(C_{1-8})alkanyl and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiazolyl; wherein phenyl, naphthyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl, thioureido, and fluoro(C_{1-6})alkanyloxy; alternatively, when phenyl and heteroaryl are optionally substituted with alkanyl or alkanyloxy substituents attached to adjacent carbon atoms, the two substituents can together form a fused cyclic alkanyl or cycloheteroalkanyl selected from the group consisting of -$(CH_2)_{3-5}$- , -O$(CH_2)_{2-4}$- , -$(CH_2)_{2-4}$O -, and -O$(CH_2)_{1-3}$O-;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl(C_{2-6})alkynyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, aminocarbonyl, C_{1-6}alkanylaminocarbonyl, di(C_{1-6}alkanyl)aminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, mercapto, aminothiocarbonyl, amidino, hydroxyamidino, phenylcarbonyl, -C(=NOH)phenyl, aminomethyl, hydroxymethyl, methanesulfonylamino, C_{6-10}arylamino (wherein C_{6-10}aryl is optionally substituted with one to three substitutents independently selected from the group consisting of C_{1-6}alkanyl,

C_{1-6}alkoxy, halogen, and hydroxy), dihydroimidazolyl, formylamino, thioformylamino, pyridinylamino, cyano, hydroxycarbonyl, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, thienyl, fluoroalkanyl and fluoroalkanyloxy; or optionally, when R_4 is two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the fused moiety is selected from the group consisting of $-(CH_2)_{3-5}-$, $-O(CH_2)_{2-4}-$, $-(CH_2)_{2-4}O-$, $-O(CH_2)_{1-3}O-$ and $-S-C(NH_2)=N-$;

R_5 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl and fluoro(C_{1-6})alkanyloxy;

A is absent or $-(CH_2)_m-$, wherein m is 2 or 3;

Y is $-(CH_2)_nX-$ or $-X(CH_2)_n-$;

X is O or S

n is 0 or 1;

Z is O, S, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl); and enantiomers, diastereomers, tautomers, solvates, or pharmaceutically acceptable salts thereof.

Finally, the present invention is directed to veterinary and pharmaceutical compositions containing compounds of Formula (I) and Formula (Ib) wherein the compositions are used to treat mild to severe pain in warm-blooded animals.

DETAILED DESCRIPTION OF THE INVENTION

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

"C_{a-b}" (where *a* and *b* are integers) refers to a radical containing from *a* to *b* carbon atoms inclusive. For example, C_{1-3} denotes a radical containing 1, 2 or 3 carbon atoms

"Alkyl:" refers to a saturated or unsaturated, branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane, alkene or alkyne. Typical alkyl groups include, but are not limited to, methyl; ethyls such as ethanyl, ethenyl, ethynyl; propyls such as propan-1-yl, propan-2-yl , cyclopropan-1-yl, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl, prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the like. Where specific levels of saturation are intended, the nomenclature "alkanyl", "alkenyl" and/or "alkynyl" is used, as defined below. In preferred embodiments, the alkyl groups are (C_1-C_6) alkyl, with (C_1-C_3) being particularly preferred.

"Alkanyl:" refers to a saturated branched, straight-chain or cyclic monovalent hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent alkane. Typical alkanyl groups include, but are not limited to, methanyl; ethanyl; propanyls such as propan-1-yl, propan-2-yl, cyclopropan-1-yl, etc.; butyanyls such as butan-1-yl, butan-2-yl, 2-methyl-propan-1-yl, 2-methyl-propan-2-yl, cyclobutan-1-yl, etc.; and the like.

In preferred embodiments, the alkanyl groups are (C_{1-8}) alkanyl, with (C_{1-3}) being particularly preferred.

"Alkenyl" refers to an unsaturated branched, straight-chain or cyclic monovalent hydrocarbon radical having at least one carbon-carbon double bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkene. The radical may be in either the cis or trans conformation about the double bond(s). Typical alkenyl groups include, but are not limited to, ethenyl; propenyls such as prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl, prop-2-en-2-yl, cycloprop-1-en-1-yl; cycloprop-2-en-1-yl; butenyls such as but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl, cyclobut-1-en-1-yl, cyclobut-1-en-3-yl, cyclobuta-1,3-dien-1-yl, etc.; and the like.

"Alkynyl" refers to an unsaturated branched, straight-chain or cyclic monovalent hydrocarbon radical having at least one carbon-carbon triple bond derived by the removal of one hydrogen atom from a single carbon atom of a parent alkyne. Typical alkynyl groups include, but are not limited to, ethynyl; propynyls such as prop-1-yn-1-yl, prop-2-yn-1-yl, etc.; butynyls such as but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl, etc.; and the like.

"Heteroalkyl" and Heteroalkanyl" refer to alkyl or alkanyl radicals, respectively, in which one or more carbon atoms (and any necessary associated hydrogen atoms) are independently replaced with the same or different heteroatoms (including any necessary hydrogen or other atoms). Typical heteroatoms to replace the carbon atom(s) include, but are not limited to, N, P, O, S, Si, etc. Preferred heteroatoms are O, N and S. Thus, heteroalkanyl radicals can contain one or more of the same or different heteroatomic groups, including, by way of example and not limitation, epoxy (–O–), epidioxy (–O–O–), thioether (–S–), epidithio (–SS–), epoxythio (–O–S–), epoxyimino (–O–NR'–), imino (–NR'–), biimino (–NR'–NR'–), azino

(=N-N=), azo (-N=N-), azoxy (-N-O-N-), azimino (-NR'-N=N-), phosphano (–PH–), λ^4–sulfano (–SH_2–), sulfonyl (-$S(O)_2$-), and the like, where each R' is independently hydrogen or (C_1–C_6) alkyl.

"Parent Aromatic Ring System:" refers to an unsaturated cyclic or polycyclic ring system having a conjugated π electron system. Specifically included within the definition of "parent aromatic ring system" are fused ring systems in which one or more rings are aromatic and one or more rings are saturated or unsaturated, such as, for example, indane, indene, phenalene, etc. Typical parent aromatic ring systems include, but are not limited to, aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*–indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta–2,4–diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene, and the like

"Aryl:" refers to a monovalent aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. Typical aryl groups include, but are not limited to, radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, *as*-indacene, *s*–indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta–2,4–diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, trinaphthalene, and the like. In preferred embodiments, the aryl group is (C_{5-20}) aryl, with (C_{5-10}) being particularly preferred. Particularly preferred aryl groups are phenyl and naphthyl groups.

"Arylalkyl:" refers to an acyclic alkyl group in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal carbon atom, is replaced

with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, 2-phenylethen-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, 2-naphthylethen-1-yl, naphthobenzyl, 2–naphthophenylethan-1-yl and the like. Where specific alkyl moieties are intended, the nomenclature arylalkanyl, arylakenyl and/or arylalkynyl is used. [In preferred embodiments, the arylalkyl group is (C_{6-26}) arylalkyl, *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_{1-6}) and the aryl moiety is (C_{5-20}). In particularly preferred embodiments the arylalkyl group is (C_{6-13}), *e.g.*, the alkanyl, alkenyl or alkynyl moiety of the arylalkyl group is (C_{1-3}) and the aryl moiety is (C_{5-10}). Even more preferred arylalkyl groups are phenylalkanyls.

"Alkanyloxy:" refers to a saturated branched, straight-chain or cyclic monovalent hydrocarbon alcohol radical derived by the removal of the hydrogen atom from the hydroxide oxygen of the alcohol. Typical alkanyloxy groups include, but are not limited to, methanyloxy; ethanyloxy; propanyloxy groups such as propan-1-yloxy ($CH_3CH_2CH_2O$-), propan-2-yloxy (($CH_3)_2CHO$-), cyclopropan-1-yloxy, etc.; butanyloxy groups such as butan-1-yloxy, butan-2-yloxy, 2-methyl-propan-1-yloxy, 2-methyl-propan-2-yloxy, cyclobutan-1-yloxy, etc.; and the like. In preferred embodiments, the alkanyloxy groups are (C_{1-8}) alkanyloxy groups, with (C_{1-3}) being particularly preferred.

"Parent Heteroaromatic Ring System:" refers to a parent aromatic ring system in which one carbon atom is replaced with a heteroatom. Heteratoms to replace the carbon atoms include N, O, and S. Specifically included within the definition of "parent heteroaromatic ring systems" are fused ring systems in which one or more rings are aromatic and one or more rings are saturated or unsaturated, such as, for example, arsindole, chromane, chromene, indole, indoline, xanthene, etc. Typical parent heteroaromatic ring systems include, but are not limited to, carbazole, imidazole, indazole, indole, indoline, indolizine, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole,

naphthyridine, oxadiazole, oxazole, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like.

"Heteroaryl:" refers to a monovalent heteroaromatic radical derived by the removal of one hydrogen atom from a single atom of a parent heteroaromatic ring system. Typical heteroaryl groups include, but are not limited to, radicals derived from carbazole, imidazole, indazole, indole, indoline, indolizine, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazole, xanthene, and the like. In preferred embodiments, the heteroaryl group is a 5–20 membered heteroaryl, with 5–10 membered heteroaryl being particularly preferred.

"Cycloheteroalkyl:" refers to a saturated or unsaturated monocyclic or bicyclic alkyl radical in which one carbon atom is replaced with N, O or S. In certain specified embodiments the cycloheteroalkyl may contain up to four heteroatoms independently selected from N, O or S. Typical cycloheteroalkyl moieties include, but are not limited to, radicals derived from imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, and the like. In preferred embodiments, the cycloheteroalkyl is a 3-6 membered cycloheteroalkyl.

"Cycloheteroalkanyl:" refers to a saturated monocyclic or bicyclic alkanyl radical in which one carbon atom is replaced with N, O or S. In certain specified embodiments the cycloheteroalkanyl may contain up to four heteroatoms independently selected from N, O or S. Typical cycloheteroalkanyl moieties include, but are not limited to, radicals derived from imidazolidine, morpholine, piperazine, piperidine, pyrazolidine, pyrrolidine, quinuclidine, and

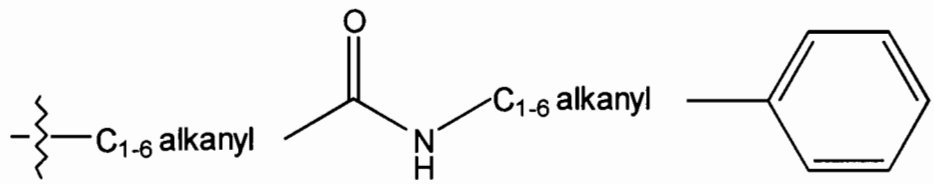
the like. In preferred embodiments, the cycloheteroalkanyl is a 3-6 membered cycloheteroalkanyl.

"Cycloheteroalkenyl:" refers to a saturated monocyclic or bicyclic alkenyl radical in which one carbon atom is replaced with N, O or S. In certain specified embodiments the cycloheteroalkenyl may contain up to four heteroatoms independently selected from N, O or S. Typical cycloheteroalkenyl moieties include, but are not limited to, radicals derived from imidazoline, pyrazoline, pyrroline, indoline, pyran, and the like. In preferred embodiments, the cycloheteroalkanyl is a 3-6 membered cycloheteroalkanyl.

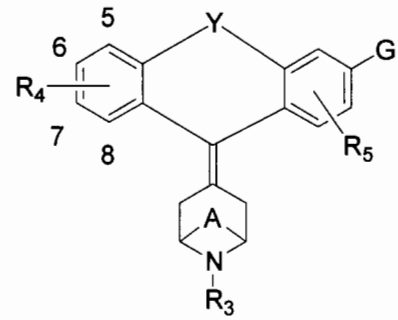
"Substituted:" refers to a radical in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s). Typical substituents include, but are not limited to, –X, –R, $–O^-$, =O, –OR, –O–OR, –SR, $–S^-$, =S, –NRR, =NR, $–CX_3$, –CN, –OCN, –SCN, –NCO, –NCS, –NO, $–NO_2$, $=N_2$, $–N_3$, –NHOH, $–S(O)_2O^-$, $–S(O)_2OH$, $–S(O)_2R$, $–P(O)(O^-)_2$, $–P(O)(OH)_2$, –C(O)R, –C(O)X, –C(S)R, –C(S)X, –C(O)OR, $–C(O)O^-$, –C(S)OR, –C(O)SR, –C(S)SR, –C(O)NRR, –C(S)NRR and –C(NR)NRR, where each X is independently a halogen (preferably –F, –Cl or –Br) and each R is independently –H, alkyl, alkanyl, alkenyl, alkynyl, alkylidene, alkylidyne, aryl, arylalkyl, arylheteroalkyl, heteroaryl, heteroarylalkyl or heteroaryl-heteroalkyl, as defined herein. Preferred substituents include hydroxy, halogen, C_{1-8}alkyl, C_{1-8}alkanyloxy, fluorinated alkanyloxy, fluorinated alkyl, C_{1-8}alkylthio, C_{3-8}cycloalkyl, C_{3-8}cycloalkanyloxy, nitro, amino, C_{1-8}alkylamino, C_{1-8}dialkylamino, C_{3-8}cycloalkylamino, cyano, carboxy, C_{1-7}alkanyloxycarbonyl, C_{1-7}alkylcarbonyloxy, formyl, carbamoyl, phenyl, aroyl, carbamoyl, amidino, (C_{1-8}alkylamino)carbonyl, (arylamino)carbonyl and aryl(C_{1-8}alkyl)carbonyl.

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.

Throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. Thus, for example, a "phenylC_{1-6}alkanylaminocarbonylC_{1-6}alkyl" substituent refers to a group of the formula

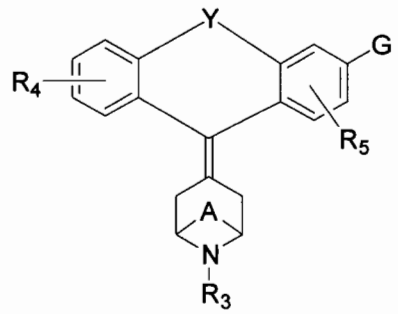


An embodiment of the present invention is directed to a compound of Formula (I) and Formula (Ib) wherein the structure is numbered as defined herein.



Formula (I) and Formula (Ib)

The present invention is directed to analgesic and anti-pyretic uses of compositions comprising a compound of Formula (I):



Formula (I)

wherein:

G is $-C(Z)NR_1R_2$, C_{6-10}aryl, C_{6-10}arylthio, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, indazolyl, indolyl, indolinyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, and pyridinyl; wherein the C_{6-10}aryl group in the C_{6-10}aryl-containing substituents of G and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, nitro, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, C_{1-8}alkanylsulfonylamino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

R_1 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, and C_{2-8}alkynyl;

R_2 is a substituent selected from the group consisting of hydrogen; C_{1-8}alkanyl; C_{2-8}alkenyl; C_{2-8}alkynyl; C_{6-10}aryl; and C_{3-8}cycloalkanyl; provided that when Z is O or S, R_2 is other than hydrogen or unsubstituted C_{1-8}alkanyl; and, wherein C_{1-8}alkanyl of

R_2 is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanyloxy, C_{1-6}alkanylthio, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, C_{1-6}alkanyloxycarbonyl, and aryloxy; wherein the phenyl and aryloxy substituents of C_{1-8}alkanyl are optionally further substituted with, and the C_{6-10}aryl and C_{3-8}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, trifluoromethyl, trifluoromethoxy, phenyl, halogen, cyano, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with one to three C_{1-4}alkanyl or C_{1-4}alkanyloxy substituents) and one to two additional substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

or, R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

R_3 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, halo$_{1-3}$(C_{1-8})alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkanyl, cycloalkanyl(C_{1-8})alkanyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, C_{1-8}alkanyloxycarbonyl, halo$_{1-3}$(C_{1-8})alkanylcarbonyl, formyl, thioformyl, carbamimidoyl, phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, phenyl(C_{1-8})alkenyl,

phenyl(C_{1-8})alkynyl, naphthyl(C_{1-8})alkanyl and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thiophenyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiazolyl; wherein phenyl, naphthyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl, thioureido, and fluoro(C_{1-6})alkanyloxy; alternatively, when phenyl and heteroaryl are optionally substituted with alkanyl or alkanloxy substituents attached to adjacent carbon atoms, the two substituents can together form a fused cyclic alkanyl or cycloheteroalkanyl selected from the group consisting of -$(CH_2)_{3-5}$- , -O$(CH_2)_{2-4}$- , -$(CH_2)_{2-4}$O -, and -O$(CH_2)_{1-3}$O-;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl(C_{2-6})alkynyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, aminocarbonyl, C_{1-6}alkanylaminocarbonyl, di(C_{1-6}alkanyl)aminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, mercapto, aminothiocarbonyl, amidino, hydroxyamidino, phenylcarbonyl, -C(=NOH)phenyl, aminomethyl, hydroxymethyl, methanesulfonylamino, C_{6-10}arylamino (wherein C_{6-10}aryl is optionally substituted with one to three substitutents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkoxy, halogen, and hydroxy), dihydroimidazolyl,

formylamino, thioformylamino, pyridinylamino, cyano, hydroxycarbonyl, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, thienyl, fluoroalkanyl and fluoroalkanyloxy; or optionally, when R_4 is two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the fused moiety is selected from the group consisting of $-(CH_2)_{3-5}-$, $-O(CH_2)_{2-4}-$, $-(CH_2)_{2-4}O-$, $-O(CH_2)_{1-3}O-$ and $-S-C(NH_2)=N-$;

R_5 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl and fluoro(C_{1-6})alkanyloxy;

A is absent or $-(CH_2)_m-$, wherein m is 2 or 3;

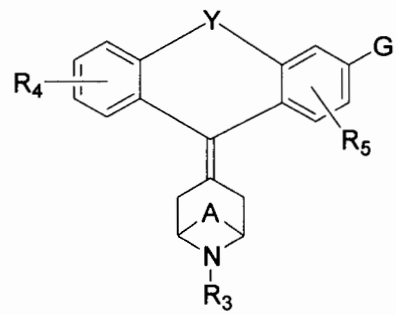
Y is $-(CH_2)_nX-$ or $-X(CH_2)_n-$;

X is O or S

n is 0 or 1;

Z is O, S, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl); and enantiomers, diastereomers, tautomers, solvates, or pharmaceutically acceptable salts thereof.

The present invention is also directed to analgesic and anti-pyretic uses of compositions comprising a compound of Formula (Ib):



Formula (Ib)

wherein:

G is bromo, chloro, cyano, trifluoromethanesulfonyloxy, C_{1-8}alkanyloxycarbonyl, carboxy, $-C(Z)NR_1R_2$, C_{6-10}aryl, C_{6-10}arylthio, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, indazolyl, indolyl, indolinyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, and pyridinyl; wherein the C_{6-10}aryl group in the C_{6-10}aryl-containing substituents of G and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, nitro, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, C_{1-8}alkanylsulfonylamino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

R_1 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, and C_{2-8}alkynyl;

R_2 is a substituent selected from the group consisting of hydrogen; C_{1-8}alkanyl; C_{2-8}alkenyl; C_{2-8}alkynyl; C_{6-10}aryl; and C_{3-8}cycloalkanyl; provided that when Z is O or S, R_2 is other than

hydrogen or unsubstituted C_{1-8}alkanyl; and, wherein C_{1-8}alkanyl of R_2 is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanyloxy, C_{1-6}alkanylthio, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, C_{1-6}alkanyloxycarbonyl, and aryloxy; wherein the phenyl and aryloxy substituents of C_{1-8}alkanyl are optionally further substituted with, and the C_{6-10}aryl and C_{3-8}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, trifluoromethyl, trifluoromethoxy, phenyl, halogen, cyano, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with one to three C_{1-4}alkanyl or C_{1-4}alkanyloxy substituents) and one to two additional substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

or, R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

R_3 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, halo$_{1-3}$(C_{1-8})alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkanyl, cycloalkanyl(C_{1-8})alkanyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, C_{1-8}alkanyloxycarbonyl, halo$_{1-3}$(C_{1-8})alkanylcarbonyl, formyl, thioformyl, carbamimidoyl,

phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, phenyl(C_{1-8})alkenyl, phenyl(C_{1-8})alkynyl, naphthyl(C_{1-8})alkanyl and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thiophenyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiazolyl; wherein phenyl, naphthyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl, thioureido, and fluoro(C_{1-6})alkanyloxy; alternatively, when phenyl and heteroaryl are optionally substituted with alkanyl or alkanyloxy substituents attached to adjacent carbon atoms, the two substituents can together form a fused cyclic alkanyl or cycloheteroalkanyl selected from the group consisting of -$(CH_2)_{3-5}$- , -O$(CH_2)_{2-4}$- , -$(CH_2)_{2-4}$O -, and -O$(CH_2)_{1-3}$O-;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl(C_{2-6})alkynyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, aminocarbonyl, C_{1-6}alkanylaminocarbonyl, di(C_{1-6}alkanyl)aminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, mercapto, aminothiocarbonyl, amidino, hydroxyamidino, phenylcarbonyl, -C(=NOH)phenyl, aminomethyl, hydroxymethyl, methanesulfonylamino, C_{6-10}arylamino (wherein C_{6-10}aryl is optionally substituted with one to three substitutents independently selected from the group consisting of C_{1-6}alkanyl,

C_{1-6}alkoxy, halogen, and hydroxy), dihydroimidazolyl, formylamino, thioformylamino, pyridinylamino, cyano, hydroxycarbonyl, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, thienyl, fluoroalkanyl and fluoroalkanyloxy; or optionally, when R_4 is two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the fused moiety is selected from the group consisting of $-(CH_2)_{3-5}-$, $-O(CH_2)_{2-4}-$, $-(CH_2)_{2-4}O-$, $-O(CH_2)_{1-3}O-$ and $-S-C(NH_2)=N-$;

R_5 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl and fluoro(C_{1-6})alkanyloxy;

A is absent or $-(CH_2)_m-$, wherein m is 2 or 3;

Y is $-(CH_2)_nX-$ or $-X(CH_2)_n-$;

X is O or S

n is 0 or 1;

Z is O, S, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl); and enantiomers, diastereomers, tautomers, solvates, or pharmaceutically acceptable salts thereof.

Embodiments of the present invention include compounds of Formula (I) wherein, preferably:

a) G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group

consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, aminocarbonyl, aminothiocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

b) G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group consisting of imidazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkanyl, C_{1-4}alkanyloxy, hydroxy(C_{1-4})alkanyl, carboxy(C_{1-4})alkanyl, C_{1-4}alkanylcarbonylamino, hydroxy, cyano, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, aminocarbonyl, aminothiocarbonyl, C_{1-8}alkanylaminocarbonyl, and di(C_{1-8}alkanyl)aminocarbonyl;

c) G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group consisting of imidazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, thienyl, isothiazolyl, isoxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkanyl, C_{1-4}alkanyloxy, hydroxy(C_{1-4})alkanyl, C_{1-4}alkanylcarbonylamino, hydroxy, cyano, oxo, thioxo, and aminocarbonyl;

d) R_1 is a substituent selected from the group consisting of hydrogen and

C_{1-4}alkanyl;

e) R_1 is selected from the group consisting of hydrogen, methyl, ethyl, and propyl;

f) R_1 is selected from the group consisting of hydrogen, methyl, or ethyl;

g) R_2 is selected from the group consisting of hydrogen; C_{1-4}alkanyl; phenyl; and C_{3-6}cycloalkanyl; provided that when Z is O or S, R_2 is other than hydrogen or unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-4}alkanyloxy, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl and C_{3-6}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{1-8}alkanyloxy, trifluoromethyl, phenyl, fluoro, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino; or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with C_{1-4}alkanyloxy or hydroxy), C_{1-4}alkanyl, or hydroxy;

h) R_2 is selected from the group consisting of C_{1-4}alkanyl, phenyl, and C_{3-6}cycloalkanyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro,

hydroxy, and C_{1-6}alkanylthio; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-4}alkanyl and hydroxy;

i) R_2 is selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, and hydroxy; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-3}alkanyl and hydroxy;

j) R_3 is selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, thioformyl, phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, and heteroaryl(C_{1-8})alkanyl wherein heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, indolyl, indolinyl, isoquinolinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl; wherein phenyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyloxy and hydroxy; or optionally, when phenyl and heteroaryl are optionally substituted with two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the moiety is selected from $-O(CH_2)_{1-3}O-$;

k) R_3 is selected from the group consisting of hydrogen, methyl, allyl, 2-methyl-allyl, propynyl, hydroxyethyl, methylthioethyl, methoxyethyl, thioformyl, phenyliminomethyl, phenethyl, and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl; wherein the phenyl in any phenyl-containing substituent is optionally substituted with one hydroxyl group;

l) R_3 is hydrogen, methyl, allyl, or heteroarylmethyl wherein heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, and thienyl;

m) R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{1-6}alkanyloxy, aminocarbonyl, aminothiocarbonyl, hydroxyamidino, formylamino, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, halogen, hydroxy, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, and thienyl;

n) R_4 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, hydroxy, and aminocarbonyl;

o) R_4 is one to two substituents independently selected from the group consisting of hydrogen, methyl, methoxy, bromo, fluoro, 5- or 6-phenyl, 5- or 6-pyridinyl, 5- or 6-furanyl, and hydroxy;

p) R_5 is one to two substituents independently selected from the group consisting of hydrogen and halogen;

q) R_5 is hydrogen;

r) A is absent or -$(CH_2)_2$-;

s) A is -$(CH_2)_2$-;

t) X is O or S;

u) n is 0;

v) Z is O, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl);

w) Z is O, NH, or N(OH);

x) Z is O or NH;

and combinations of a) through x) above.

One embodiment of the present invention is a compound of Formula (I) wherein:

G is –C(Z)NR_1R_2, phenyl, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, aminocarbonyl, aminothiocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

R_1 is hydrogen or C_{1-4}alkanyl;

R_2 is selected from the group consisting of hydrogen; C_{1-4}alkanyl; phenyl; and C_{3-6}cycloalkanyl; provided that when Z is O or S, R_2 is other than hydrogen or unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-4}alkanyloxy, hydroxy, fluoro, chloro, cyano,

aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl and C_{3-6}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{1-8}alkanyloxy, trifluoromethyl, phenyl, fluoro, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with C_{1-4}alkanyloxy or hydroxy), C_{1-4}alkanyl, or hydroxy;

R_3 is selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, thioformyl, phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, and heteroaryl(C_{1-8})alkanyl wherein heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, indolyl, indolinyl, isoquinolinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl; wherein phenyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyloxy and hydroxy; or optionally, when phenyl and heteroaryl are optionally substituted with two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the moiety is selected from $-O(CH_2)_{1-3}O-$;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{1-6}alkanyloxy, aminocarbonyl, aminothiocarbonyl, hydroxyamidino, formylamino, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, halogen, hydroxy, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl,

pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, and thienyl;

R_5 is one to two substituents independently selected from the group consisting of hydrogen and halogen;

A is absent or CH_2CH_2;

Y is O, S, CH_2O or OCH_2;

Z is O, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl); and

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

Another embodiment of the present invention is a compound of Formula (I) wherein:

G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group consisting of imidazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkanyl, C_{1-4}alkanyloxy, hydroxy(C_{1-4})alkanyl, carboxy(C_{1-4})alkanyl, C_{1-4}alkanylcarbonylamino, hydroxy, cyano, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, aminocarbonyl, aminothiocarbonyl, C_{1-8}alkanylaminocarbonyl, and di(C_{1-8}alkanyl)aminocarbonyl;

R_1 is selected from the group consisting of hydrogen, methyl, ethyl, and propyl;

R_2 is selected from the group consisting of C_{1-4}alkanyl, phenyl, and C_{3-6}cycloalkanyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-}

$_4$alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, hydroxy, and C_{1-6}alkanylthio; or R_1 and R_2 taken together with the nitrogen to which they are attached form pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-3}alkanyl and hydroxy;

R_3 is selected from the group consisting of hydrogen, methyl, allyl, 2-methyl-allyl, propynyl, hydroxyethyl, methylthioethyl, methoxyethyl, thioformyl, phenyliminomethyl, phenethyl, and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl wherein the phenyl in any phenyl-containing substituent is optionally substituted with one hydroxyl group;

R_4 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, hydroxy, and aminocarbonyl;

R_5 is hydrogen;

A is CH_2CH_2;

Y is O or S;

Z is O, NH, or N(OH); and

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

Another embodiment of the present invention is directed to compositions comprising a compound of Formula (I) wherein:

G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group

consisting of imidazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, thienyl, isothiazolyl, isoxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkanyl, C_{1-4}alkanyloxy, hydroxy(C_{1-4})alkanyl, C_{1-4}alkanylcarbonylamino, hydroxy, cyano, oxo, thioxo, and aminocarbonyl;

R_1 is hydrogen, methyl, or ethyl;

R_2 is selected from the group consisting of C_{1-4}alkanyl, phenyl, and C_{3-6}cycloalkanyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, hydroxy, and C_{1-6}alkanylthio; or R_1 and R_2 taken together with the nitrogen to which they are attached form pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-3}alkanyl and hydroxy;

R_3 is hydrogen, methyl, allyl, or heteroarylmethyl wherein heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, and thienyl;

R_4 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, hydroxy, and aminocarbonyl;

A is CH_2CH_2;

Y is O or S;

Z is O or NH; and

enantiomers, diasteromers, tautomers, solvates, and pharmaceutically acceptable salts thereof.

Another embodiment of the present invention is a compound of Formula (I) wherein:

G is selected from $-C(Z)NR_1R_2$, 2-methylcarbonylaminophenyl, 2-aminocarbonyl-phenyl, 1*H*-tetrazol-5-yl, 2-methyl-tetrazol-5-yl, 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl, 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl, 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl, [1,2,3,5]oxathiadiazol-2-oxo-4-yl, or pyridin-3-yl;

R_1 is hydrogen, methyl, or ethyl;

R_2 is selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, and hydroxy;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring;

R_3 is selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, thioformyl, phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, and heteroaryl(C_{1-8})alkanyl wherein heteroaryl is selected from the group consisting of hydrogen, methyl, allyl, or heteroarylmethyl; wherein heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, and

thienyl; wherein phenyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyloxy and hydroxy; or optionally, when phenyl and heteroaryl are optionally substituted with two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the moiety is selected from $-O(CH_2)_{1-3}O-$;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, hydroxy, and aminocarbonyl;

R_5 is hydrogen;

A is CH_2CH_2;

Y is O or S;

Z is O or NH; and

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

Another embodiment of the present invention is directed to compositions comprising a compound of Formula (I) wherein G is independently selected from $-C(Z)NR_1R_2$, 2-methylcarbonylaminophenyl, 2-aminocarbonyl-phenyl, 1*H*-tetrazol-5-yl, 2-methyl-tetrazol-5-yl, 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl, 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl, 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl, [1,2,3,5]oxathiadiazol-2-oxo-4-yl, and pyridin-3-yl; R_1 is hydrogen, methyl, or ethyl; R_2 is a substituent selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, and 2,6-dimethyl-phenoxy; wherein phenyl of R_2 is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-3}alkanyl, C_{1-3}alkanyloxy, or hydroxy; or R_1 and

R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-3}alkanyl and hydroxy; R_3 is a substituent selected from the group consisting of benzo[1,3]dioxol-5-ylmethyl, carbamimidoyl, 1-*H*-imidazol-4-ylmethyl, phenyliminomethyl, 1-prop-2-ynyl, thioformyl, 2-hydroxyphenyl-methyl, hydroxy-ethyl, methoxy-ethyl, 2-methyl-allyl, 2-methyl-but-2-enyl, allyl, furan-3-ylmethyl, H, Me, methylthioethyl, phenethyl, pyridin-2-yl methyl, and thiophen-2-ylmethyl; R_4 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, hydroxy, and aminocarbonyl; A is CH_2CH_2; Y is O or S; and Z is O or NH.

Another embodiment of the present invention is directed to compositions comprising a compound of Formula (I) wherein G is selected from $-C(Z)NR_1R_2$, 2-methylcarbonylaminophenyl, 2-aminocarbonyl-phenyl, 1*H*-tetrazol-5-yl, 2-methyl-tetrazol-5-yl, 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl, 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl, 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl, [1,2,3,5]oxathiadiazol-2-oxo-4-yl, or pyridin-3-yl; R_1 is hydrogen, methyl, or ethyl; R_2 is a substituent selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, and 2,6-dimethyl-phenoxy; and wherein phenyl of R_2 is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-3}alkanyl, C_{1-3}alkanyloxy, fluoro, or hydroxy; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-3}alkanyl and hydroxy; R_3 is a substituent selected from the group consisting of

benzo[1,3]dioxol-5-ylmethyl, carbamimidoyl, 1-*H*-imidazol-4-yl methyl, phenyliminomethyl, 1-prop-2-ynyl, thioformyl, 2-hydroxyphenyl-methyl, hydroxyethyl, methoxyethyl, allyl, furan-3-yl methyl, H, Me, methylthioethyl, and phenethyl; R_4 is one to two substituents independently selected from the group consisting of hydrogen, methyl, methoxy, bromo, fluoro, 5- or 6-phenyl, 5- or 6-pyridinyl, 5- or 6-furanyl, and hydroxy; A is CH_2CH_2; Y is O or S; and Z is O or NH.

Another embodiment of the present invention is directed to compositions comprising a compound of Formula (I) wherein G is selected from $-C(Z)NR_1R_2$, 2-methylcarbonylaminophenyl, 2-aminocarbonyl-phenyl, 1*H*-tetrazol-5-yl, 2-methyl-tetrazol-5-yl, 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl, 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl, 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl, [1,2,3,5]oxathiadiazol-2-oxo-4-yl, or pyridin-3-yl; R_1 is hydrogen, methyl, or ethyl; R_2 is a substituent selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, and 2,6-dimethyl-phenoxy; wherein phenyl of R_2 is optionally substituted with one to three substituents independently selected from the group consisting of C_{1-3}alkanyl, C_{1-3}alkanyloxy, fluoro, or hydroxy; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-3}alkanyl and hydroxy; R_3 is a substituent selected from the group consisting of H, benzo[1,3]dioxol-5-ylmethyl, 1-*H*-imidazol-4-yl methyl, furan-3-ylmethyl, pyridin-2-ylmethyl, and phenyliminomethyl; R_4 is a substituent independently selected from the group consisting of hydrogen, methyl, methoxy, bromo, fluoro, 5- or 6-phenyl, 5- or 6-pyridinyl, 5- or 6-furanyl, and hydroxy; A is CH_2CH_2; Y is O or S; and Z is O or NH.

Another embodiment of the present invention is directed to a compound of Formula (I) wherein R_4 is preferably substituted at the 5- or 6- position of Formula (I).

Another embodiment of the present invention is directed to compositions comprising a compound selected from the group consisting of:

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is [1,2,3,5]oxathiadiazol-2-oxo-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(3-fluorophenyl)-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl]aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-phenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminocarbonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-phenylethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-cyclohexyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-hydroxymethyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-hydroxyamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 5-ethyl-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*R*)-hydroxymethyl-2-phenyl-eth-1-yl)-aminocarbonyl ;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N, N*-diisobutylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1*S*-methoxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methoxypyridin-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4,5-dihydro-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(4-phenyl)-cyclohexyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methyl-4H-[1,2,4]triazol-5-yl;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 5-methyl-[1,2,4]oxadiazol-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-1-methoxycarbonyl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-hydroxy-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is isopropylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylmethylaminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1,4,5,6-tetrahydropyrimidin-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-aminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *C*-piperidin-1-yl-methyleneamine; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methoxyphenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is cyclopentylaminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylphenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylaminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*- bis (2,2,2-trifluoro-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is isobutylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *C*-morpholin-4-yl-methyleneamine; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-fluorophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-benzyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-methanesulfonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-fluorophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is thiophen-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methoxyphenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylmethylaminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylaminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is cyclopentylaminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[(4-trifluoromethyl)-cyclohexyl]-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methanesulfonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-2,2,2,-trifluoroethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-[(3-methoxy)phenyl]piperidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-4-fluorophenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*R*)-hydroxymethyl-3-methyl-but-1-yl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(dimethylaminocarbonylmethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*R*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*S*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylthio; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-hydroxy;R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-1,1-dimethylethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is fur-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is thien-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-4-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-pyrazol-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is methyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is 1*H*-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is methyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is 1H-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-aminocarbonyl; R_3 is *t*-butoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxyethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxyethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*, *N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*, *N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*R*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O; and

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O.

Another embodiment of the present invention is directed to compositions comprising a compound selected from the group consisting of:

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is [1,2,3,5]oxathiadiazol-2-oxo-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(3-fluorophenyl)-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl]aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-phenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminocarbonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-phenylethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-cyclohexyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-hydroxymethyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-hydroxyamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 5-ethyl-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*R*)-hydroxymethyl-2-phenyl-eth-1-yl)-aminocarbonyl ;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N, N*-diisobutylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1*S*-methoxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methoxypyridin-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4,5-dihydro-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(4-phenyl)-cyclohexyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methyl-4H-[1,2,4]triazol-5-yl;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methanesulfonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-2,2,2,-trifluoroethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-[(3-methoxy)phenyl]piperidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-4-fluorophenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(dimethylaminocarbonylmethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*R*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*S*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-1,1-dimethyl-ethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is fur-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is thien-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-4-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is 5-methoxy;R_5 is H; and Y is O;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-pyrazol-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is methyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is 1*H*-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is pyridin-2-ylmethyl;R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is 1H-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*R*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O; and

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O.

Another embodiment of the present invention is directed to compositions comprising a compound selected from the group consisting of:

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is [1,2,3,5]oxathiadiazol-2-oxo-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(3-fluorophenyl)-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl]aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-phenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminocarbonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-phenylethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-cyclohexyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-hydroxymethyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-hydroxyamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 5-ethyl-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*R*)-hydroxymethyl-2-phenyl-eth-1-yl)-aminocarbonyl ;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-2,2,2,-trifluoroethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-[(3-methoxy)phenyl]piperidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-4-fluorophenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(dimethylaminocarbonylmethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*S*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is fur-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is 5-methoxy;R_5 is H; and Y is O;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is 1*H*-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is pyridin-2-ylmethyl;R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O; and

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O.

Another embodiment of the present invention is directed to compositions comprising a compound selected from the group consisting of:

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is [1,2,3,5]oxathiadiazol-2-oxo-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(3-fluorophenyl)-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl]aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-phenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminocarbonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-phenylethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(dimethylaminocarbonylmethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is 5-methoxy;R_5 is H; and Y is O;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O; and

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O.

Another embodiment of the present invention is directed to compositions comprising a compound selected from the group consisting of:

a compound of Formula (Ib) wherein G is carboxy; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (Ib) wherein G is cyano; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is H; R_4 is 6-methoxycarbonyl;R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is bromo; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is bromo; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (Ib) wherein G is cyano; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (Ib) wherein G is cyano; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is cyano;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is cyano; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is cyano; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is carboxy; R_3 is t-butoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is carboxy;R_3 is H; R_4 is H; R_5 is H; and Y is O; and

a compound of Formula (Ib) wherein G is carboxy; R_3 is H; R_4 is H; R_5 is H; and Y is O.

Another embodiment of the present invention is a composition comprising the dextrorotatory enantiomer of a compound of formula (I), wherein said composition is substantially free from the levorotatory 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 levorotatory isomer calculated as.

$$\%\,levorotatory = \frac{(mass\,levorotatory)}{(mass\,dextrorotatory) + (mass\,levorotatory)} \times 100$$

Another embodiment of the present invention is a composition

comprising the levorotatory enantiomer of a compound of formula (I) wherein said composition is substantially free from the dextrorotatory 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 dextrorotatory isomer calculated as

$$\%\,dextrorotatory = \frac{(mass\,dextrorotatory)}{(mass\,dextrorotatory) + (mass\,levorotatory)} \times 100$$

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

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the

various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the 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 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.

Where the processes for the preparation of the compounds according to the invention give rise to 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.

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

Even though the compounds 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 or veterinary practice. Thus, the present invention is directed to pharmaceutical and veterinary compositions comprising compounds of Formula (I) and one or more pharmaceutically acceptable carriers, excipients or diluents.

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

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

Alternatively, the compounds of the general Formula (I) can be administered by inhalation 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. An alternative means of transdermal administration is by use of a skin patch. For example, they can be incorporated into a cream consisting

of an aqueous emulsion of 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.

For some applications, preferably the compositions are administered orally in the 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 or subcutaneously. 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 the invention described herein 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). 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 may also be coated with substances such as sugars or be enteric-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.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention 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. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

It is also apparent to one skilled in the art that the therapeutically effective dose for active compounds of the invention 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 an appropriate therapeutic level. The above dosages are thus exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of this invention may be administered in any of the foregoing compositions and dosage regimens or by means of those compositions and dosage regimens established in the art whenever use of the compounds of the invention as analgesics is required for a subject in need thereof.

The invention also provides a pharmaceutical or veterinary pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical and veterinary compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The compounds of the present invention may be used to treat mild to severe pain in warm-blooded animals such as humans by administration of an analgesically effective dose. The dosage range would be from about 0.1 mg to about 15,000 mg, in particular from about 50 mg to about 3500 mg or, more particularly from about 100 mg to about 1000 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 types of pain 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.

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 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, cellulites, 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, post-herpetic neuralgia, trigeminal neuralgia, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial 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.

In regard to the use of the present compounds in treatment of the disases or conditions such as those listed above, a therapeutically effective dose can be determined by persons skilled in the art by the use of established animal models. Such a dose would likely fall in the range of from about 0.01 mg to about 15,000 mg of active ingredient administered 1 to 4 times per day for an average (70 kg) human.

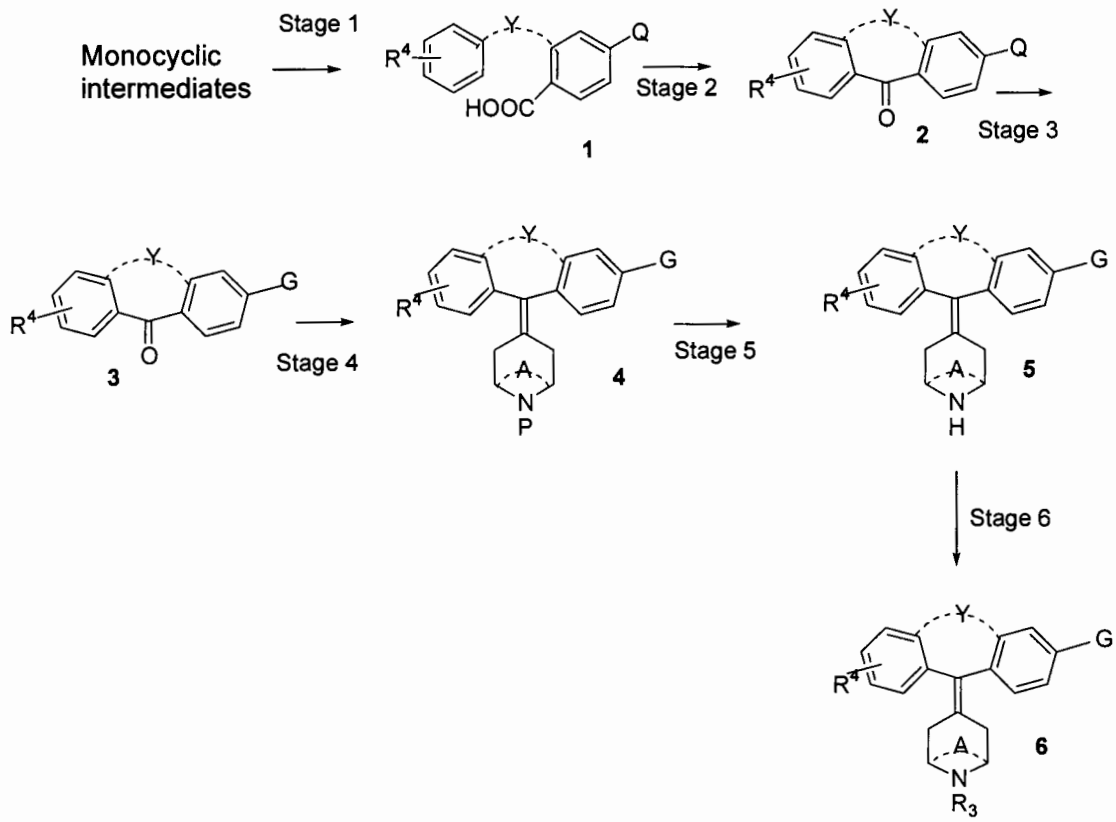
GENERAL SYNTHETIC METHODS

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

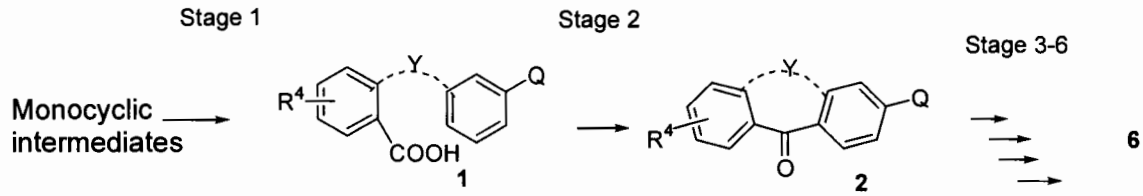
The preparation of compounds of this invention is illustrated in Schemes 1 and 2. Both schemes proceed with the same overall strategy. In stage 1, an intermediate **1** is prepared with two benzene rings connected by a linker –Y—. The linker –Y– should be of the form $-(CH_2)_n$-X– where X may be oxygen or sulfur and n may be zero or one. One benzene ring bears a group, Q, which is a group readily transformable to a substituent G as defined herein. Examples of such Q groups are fluoro, bromo, cyano, iodo, carboxy, or trifluoromethanesulfonyloxy. In some instances, the Q substituents may be the same as the G substituents of Formula (Ib). One benzene ring must bear a carboxylic acid, or a precursor to a carboxylic acid, positioned *ortho* to the linker –Y–. The atom X may be attached either to the benzene ring bearing the Q group or the benzene ring lacking the Q group. Schemes 1 and 2 differ in

that in scheme 1, the carboxylic acid is on the benzene ring bearing the Q group (**1A** and **1B**) while in scheme 2 the carboxylic acid function is on the benzene ring which does not bear the group Q (**1C, 1D** and **1E**).

Scheme 1



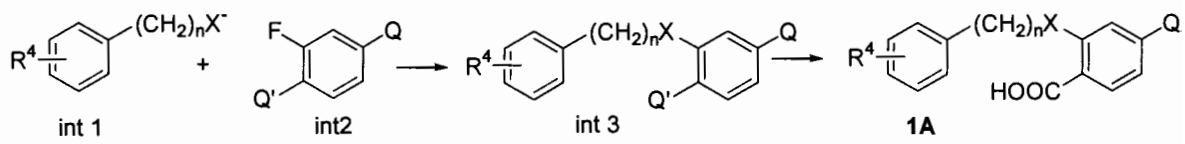
Scheme 2

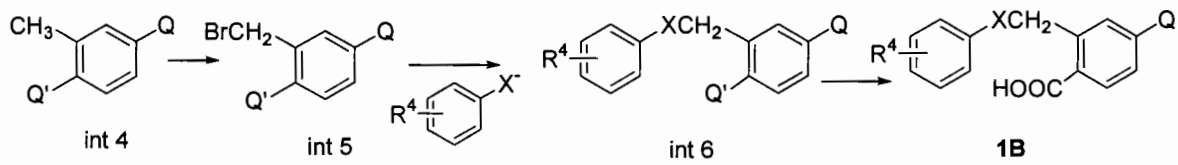


In stage 1 the linker –Y– is constructed between two monocyclic intermediates. For Scheme 1, Stage 1, the bridge may be constructed by nucleophilic aromatic displacement of fluoride from intermediate int 2 (where Q' is an electron withdrawing group, readily convertible to a carboxylic acid, for

instance cyano or carbalkoxy) by a phenoxide, thiophenoxide, benzyloxide or benzylthiooxide, int 1. The **1A** compounds are then obtained by hydrolysis with an alkali metal hydroxide. For construction of the bridge of compounds of type **1B,** a benzyl halide intermediate compound (int 5) is prepared by NBS bromination of the corresponding toluene (int 4). Reaction of int 5 with a phenoxide or phenylthiooxide leads to int 6. The **1B** compound may be obtained by alkali metal hydroxide hydrolysis of int 6.

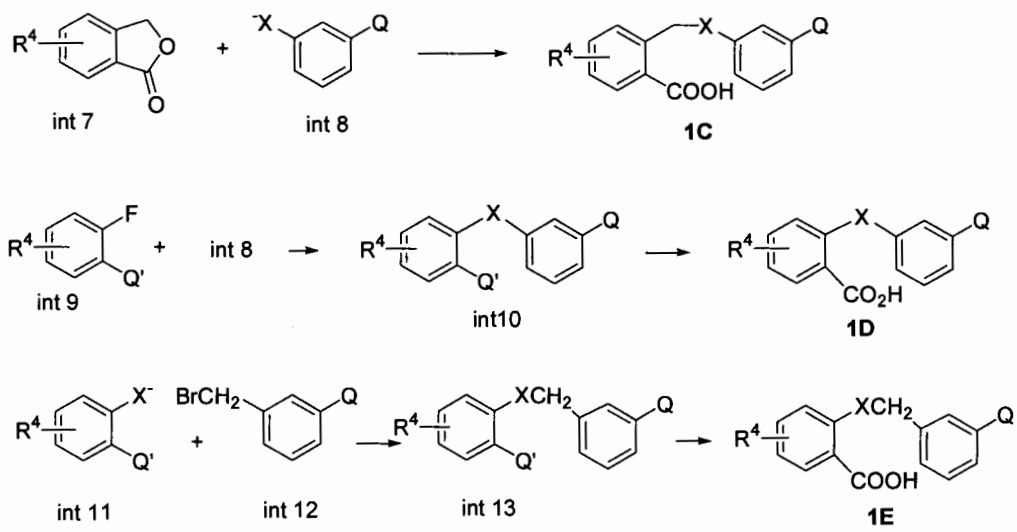
Scheme 1, Stage 1





For Scheme 2, Stage 1, in order to prepare **1C** compounds, a phthalide (int 7) may be caused to react with a phenoxide or phenylthiooxide (int 8). For preparation of compounds of formula **1D**, the bridge may be constructed by nucleophilic aromatic displacement of fluoride from intermediate int 9 by phenoxides or phenylthiooxides (int 8). The compounds of formula **1D** are then obtained by hydrolysis of int 10 with an alkali metal hydroxide. For construction of the Y-linker of compounds of intermediate 13, benzyl bromide compounds of int 12 may be reacted with a phenoxide or phenylthiooxide (int 11). The compounds of formula **1E** may then be obtained by hydrolysis of int 13 with an alkali metal hydroxide.

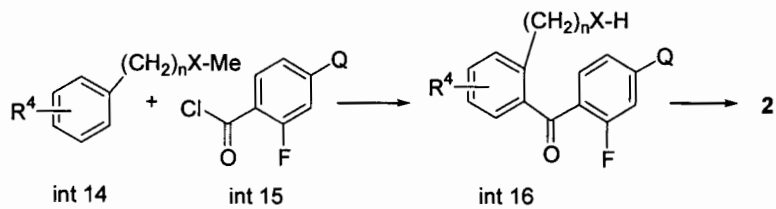
Scheme 2, Stage 1



Following Stage 1, the schemes merge. In Stage 2, compounds of formula **1** are converted by cycloacylation to ketones of formula **2**, using, for instance, $BF_3{\cdot}Et_2O$-trifluoroacetic acid or polyphosphoric acid. Alternatively, the cyclization may be effected by converting an acid of formula **1** to an acid chloride using a chlorinating agent such as thionyl chloride or the like, followed by Friedel-Crafts ring closure in the presence of a Lewis acid, such as aluminum chloride.

In addition, Stages 1 and 2 may be performed in reverse order to give compounds of formula **2** that are ready to enter Stage 3. For instance, Friedel-Crafts acylation between a methyl ether (int 14) and an appropriately substituted acid chloride provides the ketone (int 16), which is simultaneously demethylated under the reaction conditions. Subsequent formation of the bridge –Y- via a nucleophilic aromatic displacement gives compounds of formula **2** that are ready to enter Stage 3.

Scheme 3, Stages 1 and 2



In stage 3, the Q function of compounds of formula **2** is converted into group G, which may be $-C(Z)NR_1R_2$, an aryl substituent, an aryl thioether, or an appropriate heterocycle as defined herein, to give compounds of formula **3**. When the Q function of compounds of formula **2** is a halogen or trifluoromethanesulfonyloxy, it may be converted to an an ester via alkoxycarbonylation using carbon monoxide, an aliphatic alcohol, a trialkanyl amine, and a palladium catalyst such as bis(triphenylphosphine) palladium(II)dichloride. Subsequently, when Q is an ester, the ester may be hydrolyzed to a carboxylic acid. The carboxylic acid may then be coupled with an appropriately functionalized amine to form a primary, secondary or tertiary amide. Alternatively, the conversion of a carboxylic acid to an amide may be carried out via an acid chloride using thionyl chloride, oxalyl chloride, or the like, followed by a Schotten-Baumann reaction using an appropriately functionalized amine in the presence of an alkali metal hydroxide. Alternatively, the ester may be converted directly to the amide by the action of a dimethylaluminum amide.

Instead of proceeding to compounds of formula **3** *via* an ester, one may effect the transformation of the group Q to a substituent G (wherein G is an amidino or heterocycle) by way of a nitrile. Synthesis of the nitrile may be accomplished by treatment of the compounds of formula **2** (when Q is bromo or trifluoromethanesulfonyloxy) with $Zn(CN)_2$ and a palladium catalyst such as $(Ph_3P)_4Pd$ or by treatment of the compounds of formula **2** with CuCN at elevated temperatures. For the synthesis of amidino functional groups, the nitrile is treated with hydroxylamine under basic conditions to afford an oxime. Treatment of the oxime with a primary or secondary amine, CuCl, and an alkali metal carbonate under microwave irradiation in an alcoholic solvent provides the amidino compounds of the present invention. Microwave accelerated reactions may be performed using either a CEM Discover or a Personal Chemistry Smith Synthesizer microwave instrument. The oxime described above is instrumental in the preparation of compounds wherein G is a heterocycle. The oxime may be cyclized with a variety of electrophiles known to one versed in the art to give the heterocycles of the present invention. For

instance, reaction of an oxime with CDI provides oxadiazolones, and treatment of the oxime with TCDI provides the corresponding oxadiazolethiones. Similarly, the treatment of the oxime with thionyl chloride in the presence of a tertiary amine gives oxathiadiazoles of the present invention.

An aryl substituent may be installed in place of the functional group Q by coupling compounds of formula **2** (when Q is bromo or trifluoromethanesulfonyloxy) with a suitably substituted arylboronic acid in the presence of a palladium catalyst and an alkali metal carbonate.

To perform stage 4, an A-substituted ring is is attached to the tricyclic system, replacing the ketone to give compounds of formula **4** wherein m is 0, 2, or 3, as defined herein. This operation may be carried out by McMurray condensation of ketones of formula **3** with 4-piperidinones (m is 0) or 8-nortropinones (m is 2) or an azabicyclo(3.3.1)nonanone (m is 3), in the presence of a lower valent titanium reagent. Such a reagent may be formed from the addition of titanium tetrachloride to zinc dust. Alternatively, an appropriately substituted magnesium halide may be added to ketones of formula **3** to afford carbinols. Dehydration of such carbinols with acidic reagents such as formic acid, sulfuric acid or trifluoroacetic acid also gives rise to compounds of formula **4**. If desired, the operation of stages 3 and 4 may be carried out in reverse order.

As illustrated in Schemes 1 and 2, the nitrogen atoms of compounds of formula **4** may bear a group P. This group may be an alkanyl, alkenyl or aralkanyl in which case they are the therapeutically useful products of this invention. The group P may also be trifluoromethylcarbonyl, alkoxycarbonyl or aralkoxycarbonyl. The latter groupings can be converted to secondary amines of formula **5** as illustrated in Stage 5. These transformations may be carried out using certain acidic reagents such as hydrogen bromide or trimethylsilyl iodide. Or, when P is a trifluoromethylcarbonyl, basic reagents such as potassium carbonate in an alcoholic solvent may be used for the removal of P. Compounds of formula **4** bearing readily cleavable groups such as methyl, allyl or benzyl may be transformed into the aforementioned alkoxycarbonyl

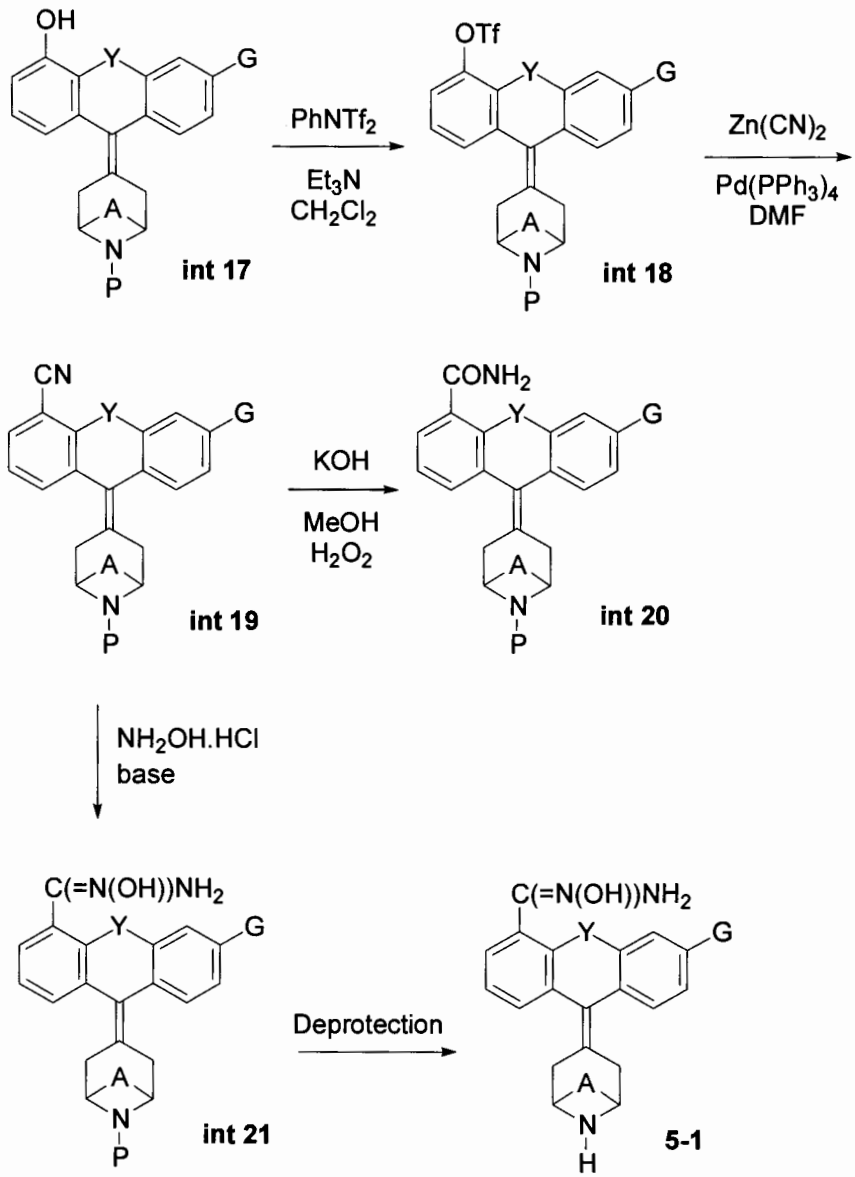
derivatives by treatment with alkanylchloro-formates such as ethyl chloroformate or 1-chloroethyl chloroformate.

Finally, the secondary amines of formula **5** may be substituted with R_3 to provide compounds of formula **6**, shown in Stage 6. These transformations may be carried out by reductive alkylation using a carbonyl-containing compound and a reducing agent such as sodium borohydride, sodium cyanoborohydride, tetramethylammonium triacetoxyborohydride, or sodium triacetoxyborohydride. Substituent R_3 may also be installed via a conventional alkyation, using an alkanyl, alkenyl or aralkyl halide and an organic or inorganic base. One skilled in the art will recognize that alkylating agents with leaving groups other than halide are equally useful for this transformation.

Desired end products of the present invention may include chemical modifications at R_4. Such transformations may include the dealkylation of lower alkyl ethers to give their corresponding alcohols, using reagents such as boron trihalides. Compounds where R_4 is a halogen atom may participate in transition metal-mediated coupling reactions such as Suzuki, Stille or Negishi chemistry.

Scheme 4 demonstrates the preparation of compounds of the present invention wherein R_4 is other than hydroxy or mercapto. A compound of formula int 17 can be converted to its triflate by treatment with N,N-bis(trifluoromethylsulfonyl)phenylamine or similar reagents to afford a compound of formula int 18. Treatment of the triflate with a cyanide source such as zinc cyanide in the presence of a palladium catalyst provides compounds of formula int 19, which subsequently can be hydrolyzed with hydroxide anion in the presence of hydrogen peroxide to afford compounds of formula int 20 wherein R_4 is an aminocarbonyl.

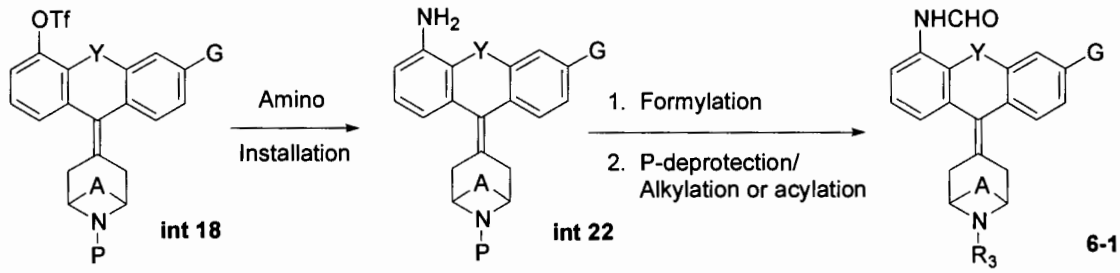
Scheme 4



The cyano group of a compound of formula int 19 is also a precursor to other R_4 substituents of the present invention. For example, a compound of formula int 19 may be treated with ammonium hydroxide in the presence of a base such as a tertiary amine to afford a hydroxyamidino compound of formula int 21. Deprotection of compounds of formula int 21 affords compounds of formula **5-1**.

As illustrated in Scheme 5, a compound of formula int 18 may be treated with an amino synthon, where a synthon is a synthetic equivalent or a functional group that is related to some other structural unit by a reliable reaction or sequence of reactions. An example of an amino group synthon includes, but is not limited to, benzophenone imine. Benzophenone imine may be used in the presence of an appropriate palladium catalyst under basic conditions, which upon treatment with ammonium hydroxide, affords compounds of formula int 22. The aniline may be formylated with acetic formic anhydride followed by removal of P using methods discussed herein. Lawesson's reagent may be used to convert carbonyl-containing R_4 substituents to their corresponding thiocarbonyl analogs.

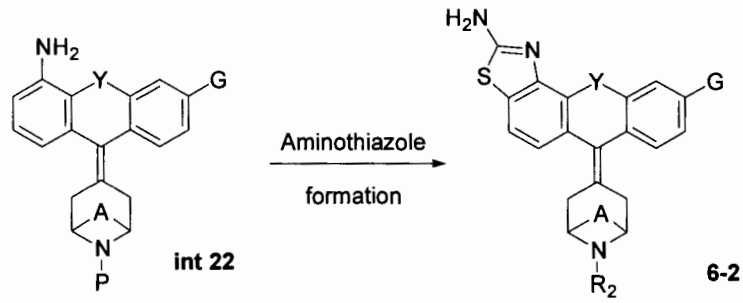
Scheme 5



The preparation of compounds wherein R_4 is $C_{6\text{-}10}$arylamino may be achieved using a palladium catalyzed amination of a compound of formula int 18 with $C_{6\text{-}10}$arylamine and an inorganic base, such as cesium carbonate.

Anilines of formula int 22 may be converted to the corresponding aminothiazoles of formula **6-2** via reaction with appropriate reagents such as potassium thiocyanate.

Scheme 6



The compounds wherein the bridge –A– is $-(CH_2)_{2-3}-$ are chiral. They may be separated into their enantiomers by chromatography on a chiral stationary phase following Stages 4, 5, or 6. Alternatively, the basic compounds of formulae **4**, **5**, and **6** may be converted to diastereomeric salts by mixture with a chiral acid and resolved into their enantiomers by fractional crystallization.

It is generally preferred that the respective product of each process step be separated from other components of the reaction mixture and subjected to purification before its use as a starting material in a subsequent step. Separation techniques typically include evaporation, extraction, precipitation and filtration. Purification techniques typically include column chromatography (Still, W. C. et. al., *J. Org. Chem.* 1978, *43*, 2921), thin-layer chromatography, crystallization and distillation. The structures of the final products, intermediates and starting materials are confirmed by spectroscopic, spectrometric and analytical methods including nuclear magnetic resonance (NMR), mass spectrometry (MS) and liquid chromatography (HPLC). In the descriptions for the preparation of compounds of this invention, ethyl ether, tetrahydrofuran and dioxane are common examples of an ethereal solvent; benzene, toluene, hexanes and heptanes are typical hydrocarbon solvents and dichloromethane and dichloroethane are representative halogenated hydrocarbon solvents. In those cases where the product is isolated as the acid addition salt the free base may be obtained by techniques known to those skilled in the art. In those cases in which the product is isolated as an acid

addition salt, the salt may contain one or more equivalents of the acid. Enantiomers of the compounds of the present invention may be separated using chiral HPLC.

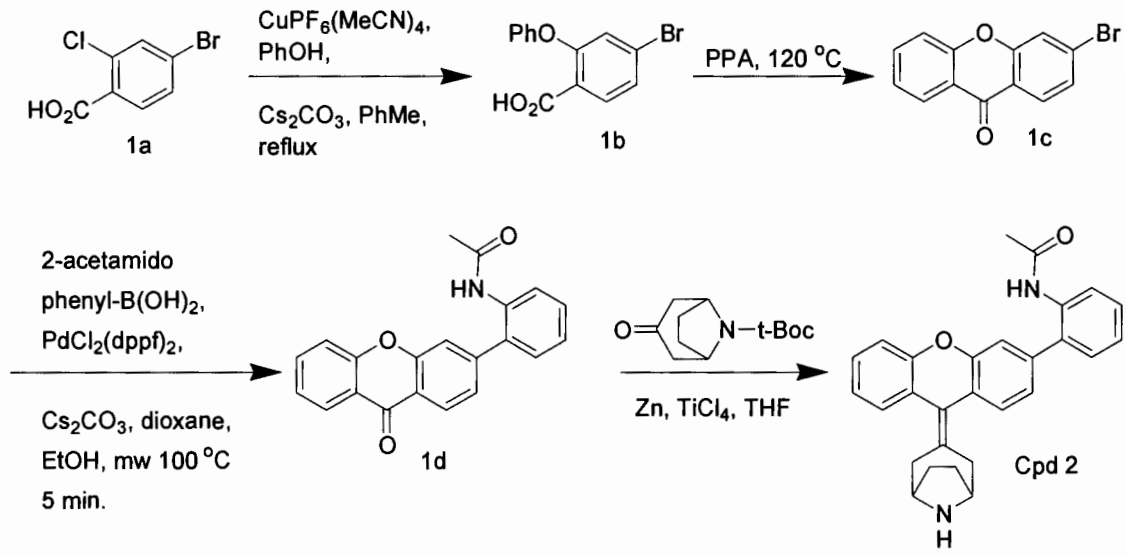
Representative compounds of the present invention can be synthesized in accordance with the general synthetic methods described above and are illustrated more particularly in the schemes that follow. Since the schemes are illustrations, the invention should not be construed as being limited by the chemical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

Abbreviations

CDI	=	1,1′-carbonyldiimidazole
DBN	=	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	=	*N*,*N*-dimethylformamide
dppf	=	1,1'-bis(diphenylphosphino)ferrocene
Et	=	ethyl
h	=	hour(s)
Me	=	methyl
min	=	minute(s)
TCDI	=	1,1′-thiocarbonyldiimidazole
PPA	=	polyphosphoric acid
t-Boc	=	*tert*-butoxycarbonyl
TCDI	=	1,1'-thiocarbonyldiimidazole
TFA	=	trifluoroacetic acid
THF	=	tetrahydrofuran
μW	=	microwave irradiation
W	=	watt(s)

EXAMPLES

Example 1



Procedure A

4-Bromo-2-phenoxybenzoic acid (1b). 4-Bromo-2-chloro-benzoic acid (10 g, 42 mmol), phenol (4.19 g, 44 mmol), tetrakisacetonitrilecopper hexafluorophosphate (3.95 g, 10.6 mmol), and cesium carbonate (27.6 g, 85 mmol) were added to a 1 L 3-neck round bottom flask equipped with a mechanical stirrer, reflux condenser, and containing toluene (350 mL). The reaction was refluxed overnight under nitrogen with stirring. After cooling, ethyl acetate (200 mL) was added and the reaction was acidified with aqueous 2N HCl. The organic phase was separated, dried ($MgSO_4$), and filtered. The filtrate was concentrated to afford 4-bromo-2-phenoxybenzoic acid (12.4 g) that was used in subsequent reactions without further purification.

Procedure B

3-Bromo-xanthen-9-one (1c). Polyphosphoric acid (260 g, 20:1; w:w) was added to 4-bromo-2-phenoxybenzoic acid (13.5 g). The reaction was heated (120°C) while being stirred briskly with a mechanical stirrer to achieve

homogeneity. After 2h, the heating apparatus was removed. Once the reaction temperature was below 70°C, the mixture was poured over crushed ice. The resulting aqueous solution was extracted with chloroform (3 x 100mL). The combined organic extracts were washed with sodium bicarbonate solution (100 mL, 1M), dried ($MgSO_4$), and concentrated to afford 3-bromo-xanthen-9-one (11.4 g) that was used in subsequent reactions without further purification.

Procedure C

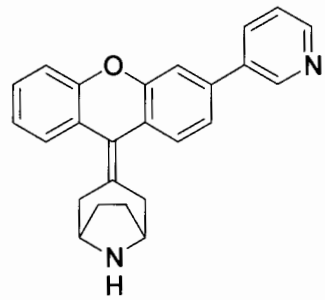
***N*-[2-(9-Oxo-9*H*-xanthen-3-yl)-phenyl]-acetamide (1d).**
3-Bromo-xanthen-9-one (0.25 g, 0.9 mmol), 2-acetamidophenylboronic acid (0.99 mmol), 1,1'-bis-(diphenylphosphino)ferrocene-palladium (II) dichloride (33 mg, 0.045 mmol), cesium carbonate (0.59 g, 1.8 mmol), dioxane (4 mL), and ethanol (2 mL) were microwaved in a 5-mL reaction vessel at 100°C for 5 min. The reaction was filtered and concentrated. The residue was purified by reverse phase chromatography to afford *N*-[2-(9-Oxo-9*H*-xanthen-3-yl)-phenyl]-acetamide.

Procedure D

***N*-{2-[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-9*H*-xanthen-3-yl]-phenyl}-acetamide (Cpd 2).** A suspension of zinc powder (0.317 g, 4.8 mmol) in THF (100 mL) at ambient temperature was treated with titanium(IV)chloride (0.266 mL, 2.4 mmol) by dropwise addition. The resultant mixture was heated at reflux for 2 h under a nitrogen atmosphere. The resultant solution was cooled to room temperature. A portion of 3-oxo-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester (0.136 g, 0.6 mmol) and *N*-[2-(9-oxo-9H-xanthen-3-yl)-phenyl]-acetamide (0.20 g, 0.6 mmol) were added and the solution was heated at reflux for 2 h. The reaction was diluted with ethyl acetate (15 mL) and aqueous 1N hydrochloric acid (20 mL). The organic layer was separated, dried ($MgSO_4$), and filtered. The filtrate was evaporated in vacuo. The crude product was purified by reverse phase preparative HPLC, using a gradient of acetonitrile (10% to 90%) in water with

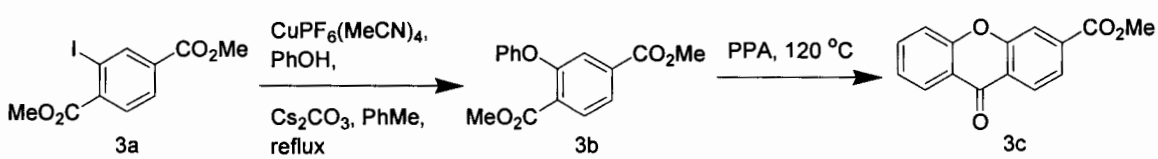
trifluoroacetic acid (0.1%), to give the trifluoroacetic acid salt of Compound **2** (0.124 g). MS *m/z* (MH^+) 423.2; ^1H NMR (DMSO-d_6) δ 1.32 (m, 2H), 1.79 (m, 2H), 1.88 (s, 3H), 2.92-3.0 (m, 4H), 4.04 (m, 2H), 7.21-7.47 (m, 11H), 8.67 (bs, 1H), 9.05 (d, 1H), 9.35 (s, 1H).

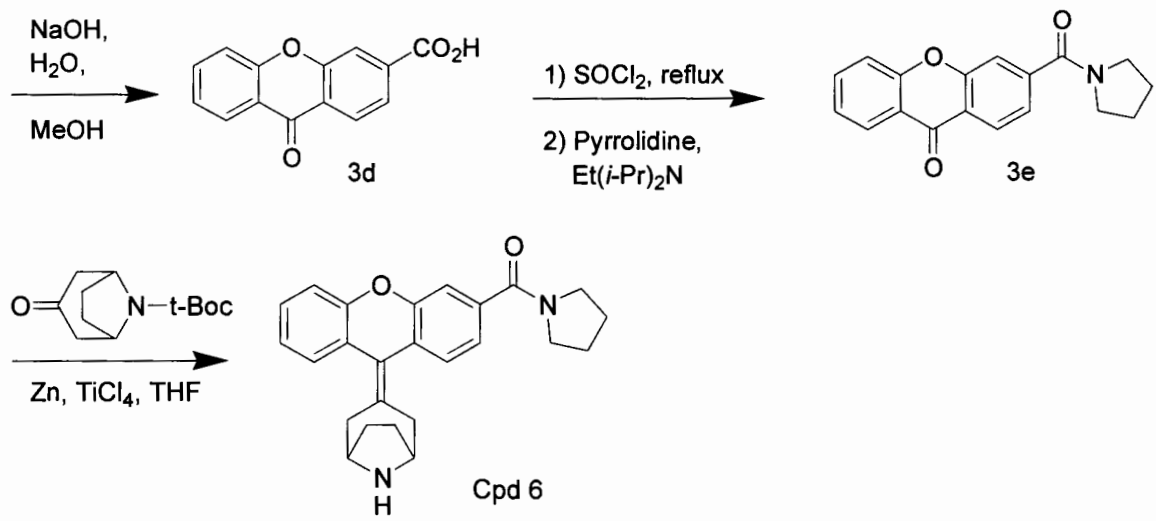
Example 2



3-(3-Pyridin-3-yl-xanthen-9-ylidene)-8-aza-bicyclo[3.2.1]octane (Cpd 12). The title compound was prepared using the method described in Example 1, substituting 3-pyridylboronic acid for 2-acetamidophenylboronic acid in Procedure C and using an adaptation of Procedure D. MS *m/z* (MH^+) 367.1; ^1H NMR (DMSO-d_6) δ 1.29 (d, 2H, J = 9.2 Hz), 1.78 (m, 2H), 2.91-3.09 (m, 4H), 4.01 (s, 2H), 7.24 (t, 1H, J = 7.4 Hz), 7.31 (d, 1H, J = 6.8 Hz), 7.38 (d, 1H, J = 7.0 Hz), 7.43 (d, 1H, J = 7.7 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.62-7.73 (m, 2H), 7.73 (s, 1H), 8.32 (d, 1H, J = 8.0 Hz), 8.68 (m, 1H), 8.81 (m, 1H), 9.05 (s, 1H), 9.11 (m, 1H).

Example 3





2-Phenoxy-terephthalic acid dimethyl ester (3b). The title compound was prepared according to the method described in Procedure A and substituting 2-iodo-terephthalic acid dimethyl ester for 4-bromo-2-chloro-benzoic acid.

9-Oxo-9H-xanthene-3-carboxylic acid methyl ester (3c). The title compound was prepared according to the method described in Procedure B, substituting 2-phenoxy-terephthalic acid dimethyl ester for 4-bromo-2-phenoxybenzoic acid.

Procedure E

9-Oxo-9*H*-xanthene-3-carboxylic acid (3d). A solution of 9-oxo-9*H*-xanthene-3-carboxylic acid methyl ester (3.75 mmol) and 3 N sodium hydroxide (4.12 mmol) in MeOH (30 mL) was heated at reflux for 2 h. The solution was cooled to rt and made acidic with 2 N hydrochloric acid. The mixture was concentrated in vacuo, and then diluted with water. The resultant solid was collected by filtration, washed with water and air-dried to yield the title compound.

Procedure F

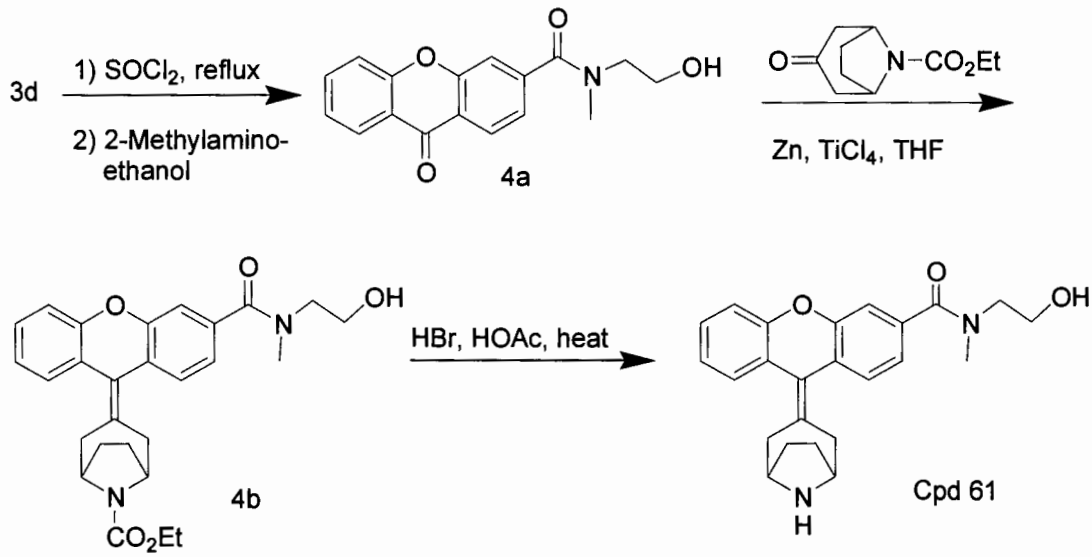
3-(Pyrrolidine-1-carbonyl)-xanthen-9-one (3e).

9-oxo-9*H*-xanthene-3-carboxylic acid (9 g, 37.4 mmol) was added to thionyl chloride (28 mL, 334 mmol). The mixture was refluxed for 5 h. At that time, the thionyl chloride was removed under vacuum and the remaining residue was

diluted with toluene and concentrated to dryness to give 9-oxo-9*H*-xanthene-3-carbonyl chloride. A portion of 9-oxo-9*H*-xanthene-3-carbonyl chloride (0.25 g, 0.96 mmol) was dissolved in acetonitrile (7 mL). Diisopropylethylamine (335 μL, 1.9 mmol) was then added to the mixture with the subsequent addition of pyrrolidine (113 μL, 1.3 mmol). After stirring 2 h, the solvent was concentrated and the residue was purified by reverse phase preparative HPLC, using a gradient of acetonitrile (10% - 90%) in water with trifluoroacetic acid (0.1%) to afford the 3-(pyrrolidine-1-carbonyl)-xanthen-9-one. MS *m/z* (MH^+) 294.1.

[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-9*H*-xanthen-3-yl]-pyrrolidin-1-yl-methanone (Cpd 6). The title compound was prepared according to Procedure D, substituting 3-(pyrrolidine-1-carbonyl)-xanthen-9-one for *N*-[2-(9-oxo-9H-xanthen-3-yl)-phenyl]-acetamide and obtained as a TFA salt after reverse phase preparative HPLC. MS *m/z* (MH^+) 387.2; ^1H NMR (DMSO-d_6) δ 1.28 (d, 2H, J = 11.2 Hz), 1.80-1.89 (m, 6H), 2.95 (q, 4H, J = 16.1 Hz), 3.41 (t, 2H, J = 6.2 Hz), 3.47 (t, 2H, J = 6.8 Hz), 4.0 (s, 2H), 7.23 (t, 1H, J = 7.3 Hz), 7.28-7.46 (m, 6H), 8.80 (bs, 1H), 9.11 (m, 1H).

Example 4



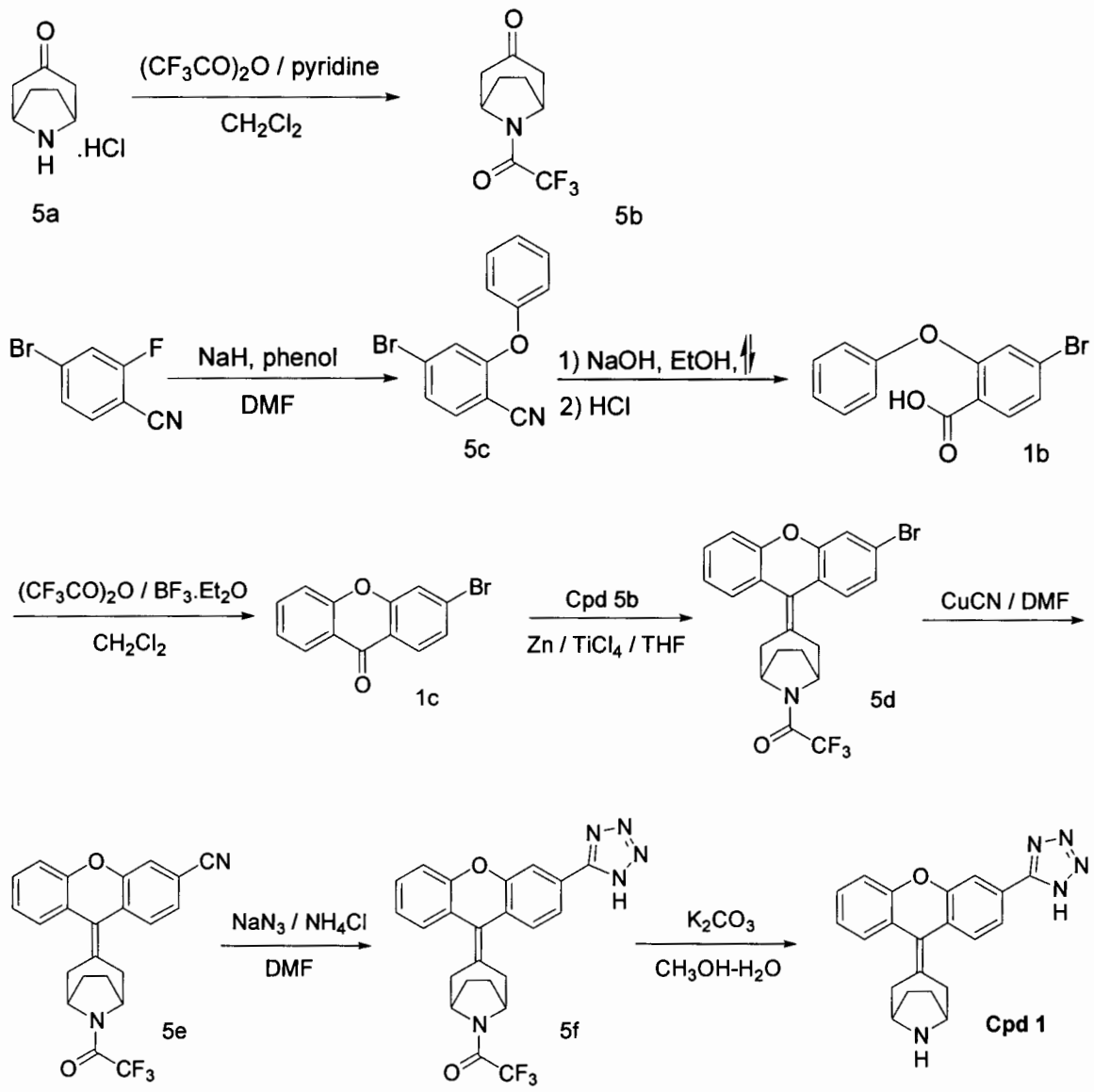
9-Oxo-9*H*-xanthene-3-carboxylic acid (2-hydroxy-ethyl)-methyl-amide (4a). Using the method described in Procedure F, substituting 2-methylamino-ethanol for pyrrolidine, the title compound **4a** was prepared.

3-{3-[(2-Hydroxyethyl)-methyl-carbamoyl]-xanthen-9-ylidene}-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (4b). Using the method described in Procedure D, substituting 9-Oxo-9*H*-xanthene-3-carboxylic acid (2-hydroxy-ethyl)-methyl-amide for *N*-[2-(9-oxo-9*H*-xanthen-3-yl)-phenyl]-acetamide and substituting 3-oxo-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid ethyl ester for 3-oxo-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester, the desired product **4b** was prepared.

Procedure G

9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-9*H*-xanthene-3-carboxylic acid (2-hydroxy-ethyl)-methyl-amide (Cpd 61). A sample of compound **4b** (0.20 g, 0.43 mmol) was dissolved in 1 mL acetic acid and 2 mL of 30% HBr in acetic acid was added to the reaction under Argon before heating at 80°C for 1 h. The reaction was cooled, added to ice cold NaOH and extracted with $CHCl_3$. The combined organic phases were concentrated. The resulting residue was purified by reverse phase HPLC, using a gradient of acetonitrile (10% to 90%) in water with trifluoroacetic acid (0.1%) to give the trifluoroacetic acid salt of compound **61** (0.146 g). MS *m/z* (MH^+) 391.0; ^1H NMR (DMSO-d_6) δ 1.26 (m, 2H), 2.93-3.04 (m, 6H), 3.28 (m, 1H), 3.49 (m, 2H), 3.61 (m, 1H), 4.00 (m, 3H), 7.21-7.42 (m, 1H, J = 7.0 Hz), 8.65 (m, 1H), 9.05 (m, 1H).

Example 5



Procedure H

8-(2,2,2-Trifluoroacetyl)-8-aza-bicyclo[3.2.1]octan-3-one (5b). To a solution of nortropinone hydrochloride (10 g, 61.87 mmol) and pyridine (20 mL, 247 mmol) in CH_2Cl_2 (120 mL) was added dropwise trifluoroacetic anhydride (12.4 mL, 87.79 mmol) at 0°C. The reaction mixture was stirred at 0°C for 1 h and at room temperature for an additional 1 h. A portion of 2N HCl (65 mL) was added to the mixture. The organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The crude compound **5b** was used in the next reaction without further purification. MS *m/z* (MH^+) 221.9; ^1H NMR ($CDCl_3$,) δ

1.78 (m, 1H), 1.90 (m, 1H), 2.19 (m, 2H), 2.49 (d, 2H), 2.72 (m, 2H), 4.71 (m, 1H), 4.99 (m, 1H).

Procedure I

4-Bromo-2-phenoxy-benzonitrile (5c). Sodium hydride (12 g, 300 mmol) (60% by wt) was weighed into a flask and washed free of oil with several hexane rinsings. The hexanes were decanted and discarded and DMF was added to the flask. A solution of phenol (23.5 g, 250 mmol) in DMF (100 mL) was added dropwise and the mixture was stirred at room temperature. To the mixture was added a solution of 4-bromo-2-fluoro-benzonitrile (50 g, 250 mmol, 100 mL DMF), dropwise. Upon complete addition, the reaction was refluxed for 20 h. The reaction was cooled to room temperature and poured into cold 1 N NaOH. A fine, tan precipitate formed and was collected by vacuum filtration to give Compound **5c**. MS *m/z* (MH^+) 277.

Procedure J

4-Bromo-2-phenoxy-benzoic acid (1b). Compound **5c** (35.3 g, 129 mmol) was added to 130 mL EtOH, followed by the addition of 340 mL of 20% aqueous NaOH. The reaction was heated to reflux for 20 h. At that time the mixture was cooled to room temperature and poured into 6 N HCl. The solid was collected by vacuum filtration, dissolved in 3:1 THF-ethyl ether, and washed with brine. The organic phase was dried ($MgSO_4$) and concentrated. The solids were dried in a vacuum oven at 60°C overnight to give the desired compound **1b**. MS *m/z* (MH^+) 292.

Procedure K

3-Bromo-xanthen-9-one (1c). To a suspension of 4-bromo-2-phenoxy-benzoic acid (5 g, 17 mmol) in CH_2Cl_2 (50 mL) was added dropwise trifluoroacetic anhydride (2.9 mL, 20.53 mmol) at room temperature. The mixture was stirred at room temperature for 5 min. To this solution was added dropwise boron trifluoride diethyl etherate (0.215 mL, 1.7 mmol) at 0°C. After 30 min, the reaction was allowed to warm to room temperature. The

mixture was stirred at room temperature for 2 h, at which time the mixture was poured into 1N NaOH (35 mL) that was cooled to about 3°C. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. Heptane was added to the residue and the resulting solid was collected by filtration to give Compound **1c**. MS *m/z* (MH^+) 276.7; ^1H NMR ($CDCl_3$,) δ 7.43 (t, 1H), 7.52 (m, 2H), 7.76 (m, 2H), 8.23 (d, 1H), 8.35 (dd, 1H).

1-[3-(3-Bromo-xanthen-9-ylidene)-8-aza-bicyclo[3.2.1]oct-8-yl]-2,2,2-trifluoro-ethanone (5d). Using the method described in Procedure D, substituting Compound **1c** for *N*-[2-(9-Oxo-9H-xanthen-3-yl)-phenyl]-acetamide and substituting Compound **5b** for 3-oxo-8-aza-bicyclo[3.2.1]octane-8-carboxylic acid tert-butyl ester, the title compound **5d** was prepared. MS *m/z* (MH^+) 463.6, 465.8; ^1H NMR($CDCl_3$,) δ 1.43 (m, 2H), 1.82 (m, 2H), 2.94 (m, 4H), 4.42 (m, 1H), 4.72 (m, 1H), 7.20 (m, 6H), 7.4 (m, 1H).

Procedure L

9-[8-(2,2,2-Trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-xanthene -3-carbonitrile (5e). To a solution of Compound **5d** (3 g, 6.46 mmol) in DMF (100 mL) was added CuCN (0.69 g, 7.70 mmol). The reaction mixture was refluxed for 2 d and then cooled to room temperature. The mixture was poured into water (100 mL), and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed sequentially with H_2O (100 mL), brine (100 mL), then dried ($MgSO_4$) and concentrated. The crude product was purified by normal phase chromatography, using a gradient of ethyl acetate (0% to10%) in heptane to give compound **5e**. MS *m/z* ($M+H^+$) 410.9; ^1H NMR ($CDCl_3$) δ 1.41 (m, 2H), 1.85 (m, 2H), 2.96 (m, 4H), 4.44 (m, 1H), 4.73 (m, 1H), 7.23 (m, 3H), 7.33 (m, 2H), 7.43 (dt, 1H), 7.51 (m, 1H).

Procedure M

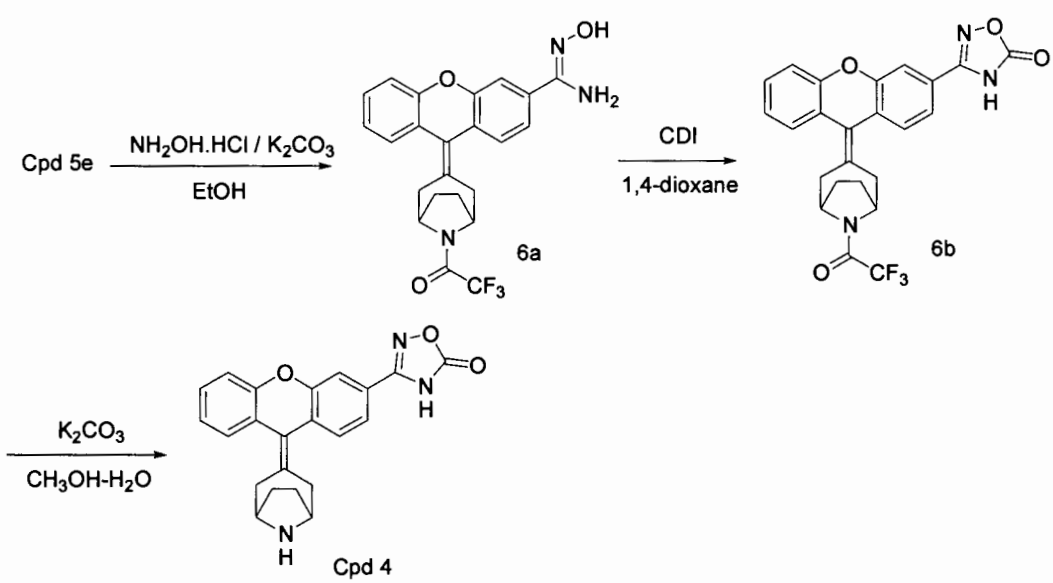
2,2,2-Trifluoro-1-{3-[3-(1*H*-tetrazol-5-yl)-xanthen-9-ylidene]-8-aza-bicyclo

[3.2.1]oct-8-yl}-ethanone (5f). To a solution of Compound **5e** (0.232 g, 0.56 mmol) in DMF (5 mL) were added NaN_3 (0.11 g, 1.69 mmol) and NH_4Cl (0.09 g, 1.68 mmol). The reaction mixture was heated at 120°C for 14 h, and then cooled to room temperature. An insoluble material was collected by filtration and washed with DMF (5 mL). The filtrate was acidified with 2N HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with H_2O (10 mL), dried ($MgSO_4$), and concentrated to give the title compound **5f** which was used for subsequent reactions without further purification. MS *m/z* (MH^+) 453.9.

Procedure N

3-[3-(1*H*-Tetrazol-5-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]octane (Cpd 1). To a solution of Compound **5f** (0.2 g, 0.44 mmol) in CH_3OH (4 mL) and H_2O (1 mL) was added K_2CO_3 (0.152 g, 1.1 mmol). The mixture was stirred at room temperature for 14 h, and was purified by reverse phase HPLC to give the title Compound **1** as a TFA salt. MS *m/z* (MH^+) 357.9; ^1H NMR (DMSO-d_6,) δ 1.27 (m, 2H), 1.77 (m, 2H), 2.97 (m, 4H), 4.00 (m, 2H), 7.36 (m, 4H), 7.63 (d, 1H), 7.91 (m, 3H), 8.82 (m, 1H), 9.17 (m, 1H).

Example 6



Procedure O

***N*-Hydroxy-9-[8-(2,2,2-trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-xanthene-3-carboxamidine (6a).** To a suspension of compound **5e** (0.44 g, 1.07 mmol) in EtOH (5 mL) were added $NH_2OH \cdot HCl$ (0.223 g, 3.19 mmol) and K_2CO_3 (0.3 g, 2.17 mmol). The reaction mixture was refluxed for 4 h. Upon cooling to room temperature, H_2O (1 mL) was added to the mixture. The mixture was extracted with CH_2Cl_2 (2 x 5mL), dried ($MgSO_4$), and concentrated to yield compound **6a**. The product **6a** was used in the next reaction without further purification. MS *m/z* (MH^+) 443.9.

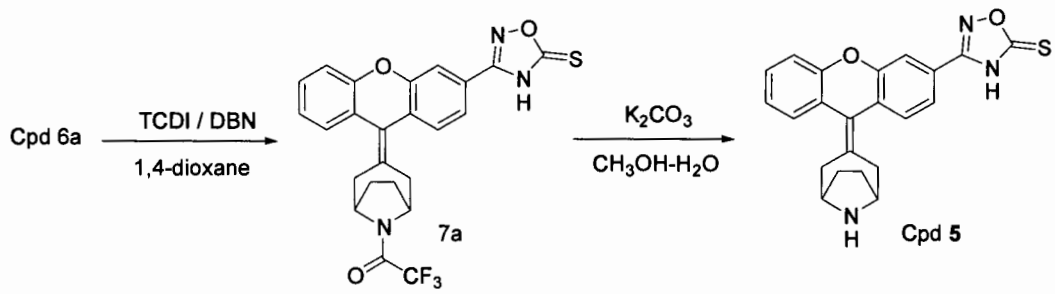
Procedure P

3-{9-[8-(2,2,2-Trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-xanthen-3-yl}-4*H*-[1,2,4]oxadiazol-5-one (6b). To a solution of compound **6a** (0.1 g, 0.23 mmol) in 1,4-dioxane (4 mL) was added 1,1'-carbonyldiimidazole (CDI, 0.055 g, 0.34 mmol). The mixture was stirred at 110°C for 40 min under a nitrogen atmosphere. After being cooled, the reaction was concentrated. The crude compound **6b** was used in the next reaction without further purification. MS *m/z* (MH^+) 469.8.

Procedure Q

3-[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-9H-xanthen-3-yl]-4H-[1,2,4]oxadiazol-5-one (Cpd 4). Using an adaptation of the method described in Procedure N and substituting compound **6b** for compound **5f**, the title compound **4** was prepared as a TFA salt. MS m/z (MH^+) 374.0; ^1H NMR (CH_3OH-d_4) δ 1.48 (m, 2H), 1.94 (m, 2H), 3.11 (m, 4H), 4.06 (m, 2H), 7.26 (m, 2H), 7.38 (m, 2H), 7.51 (d, 1H), 7.62 (m, 3H).

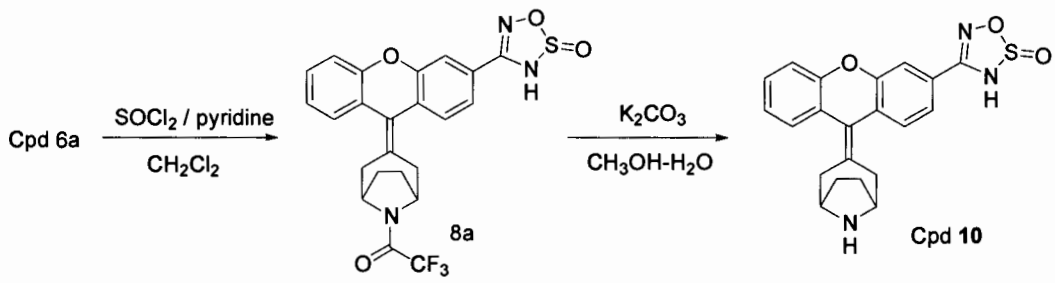
Example 7



2,2,2-Trifluoro-1-{3-[3-(5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]oct-8-yl}-ethanone (7a). Using an adaptation of Procedure P, substituting 1,1'-thiocarbonyldiimidazole (TCDI) for CDI and adding 1,8-diazabicyclo[5.4.0]undec-7-ene (DBN, 1 equivalent), the title compound **7a** was prepared. The crude compound **7a** was used in the next reaction without further purification. MS *m/z* (MH^+) 485.8.

3-[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-9*H*-xanthen-3-yl]-4H-[1,2,4]oxadiazole-5-thione (Cpd 5). Using an adaptation of the method described in Procedure N and substituting compound **7a** for compound **5f**, the title compound **5** was prepared as a TFA salt. MS *m/z* (MH^+) 389.9; ^1H NMR (CH_3OH-d_4) δ 1.47 (m, 2H), 1.93 (m, 2H), 3.10 (m, 4H), 4.06 (m, 2H), 7.27 (m, 2H), 7.37 (m, 2H), 7.53 (d, 1H), 7.67 (m, 3H).

Example 8



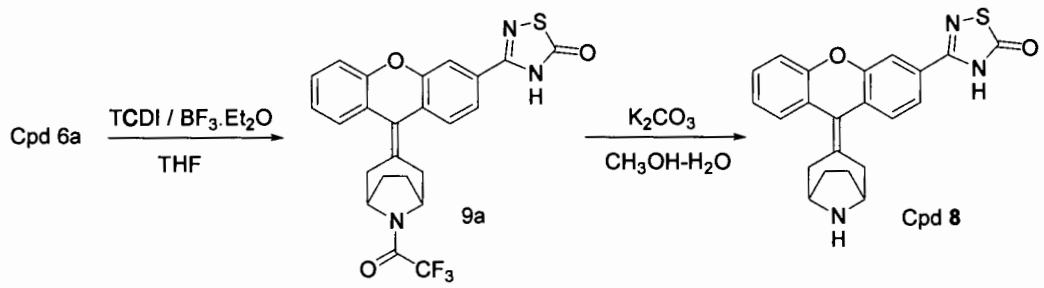
Procedure R

2,2,2-Trifluoro-1-{3-[3-(2-oxo-2,3-dihydro-2l4-[1,2,3,5]oxathiadiazol-4-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]oct-8-yl}-ethanone (8a). To a solution

of compound **6a** (0.071 g, 0.16 mmol) and pyridine (0.026 mL, 0.32 mmol) in CH_2Cl_2 (1 mL) was added dropwise a solution of thionyl chloride (0.013 mL, 0.18 mmol) in CH_2Cl_2 (1 mL) at –70°C. After being stirred for 1 h at –70°C, the mixture was allowed to warm to room temperature, and then washed sequentially with water and brine, dried ($MgSO_4$), and concentrated. The resulting compound **8a** was used in the next reaction without further purification. MS *m/z* (MH^+) 489.7.

3-[3-(2-Oxo-2,3-dihydro-2l4-[1,2,3,5]oxathiadiazol-4-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]octane (Cpd 10). Using an adaptation of the method described in Procedure N and substituting compound **8a** for compound **5f**, the title compound **10** was prepared as a TFA salt. MS m/z (MH^+) 393.9; ^1H NMR (CH_3OH-d_4 δ 1.49 (m, 2H), 1.94 (m, 2H), 3.11 (m, 4H), 4.06 (m, 2H), 7.28 (m, 2H), 7.39 (m, 2H), 7.54 (d, 1H), 7.70 (m, 3H).

Example 9



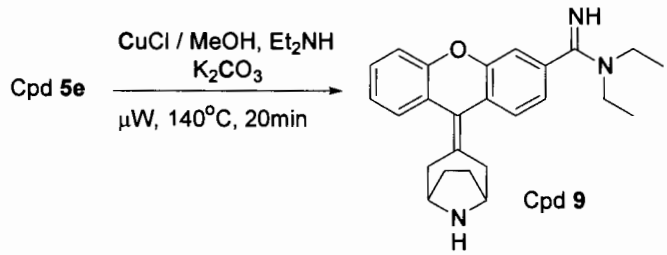
Procedure S

3-{9-[8-(2,2,2-Trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-xanthen-3-yl}-4H-[1,2,4]thiadiazol-5-one (9a). A mixture of compound **6a** (0.0417 g, 0.094 mmol) and TCDI (0.025 g, 0.14 mmol) in THF (2 mL) was stirred at room temperature for 45 min. The mixture was diluted with H_2O (2 mL) and extracted with EtOAc (3 x 5mL). The combined organic extracts were washed with H_2O (15 mL), dried ($MgSO_4$), and concentrated. The residue was dissolved in THF (2 mL). Boron trifluoride diethyl etherate was added to the solution, and the resulting mixture was stirred at room temperature for 1 h. The mixture was diluted with H_2O (2 mL) and extracted with EtOAc (3 x 5mL). The organic

layers were dried ($MgSO_4$), and concentrated. The resultant compound **9a** was used in the next reaction without further purification. MS *m/z* (MH^+) 485.8.

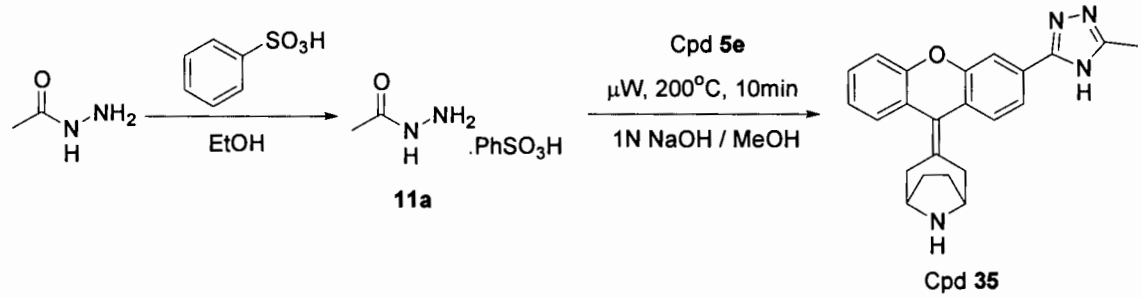
3-[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-9H-xanthen-3-yl]-4H-[1,2,4]thiadiazol-5-one (Cpd 8). Using an adaptation of the method described in Procedure N and substituting compound **9a** for compound **5f**, the title compound **8** was prepared as a TFA salt. MS *m/z* (MH^+) 389.9; ^1H NMR (CH_3OH-d_4,) δ 1.48 (m, 2H), 1.93 (m, 2H), 3.11 (m, 4H), 4.05 (m, 2H), 7.27 (m, 2H), 7.38 (m, 2H), 7.50 (d, 1H), 7.76 (m, 3H).

Example 10



9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-*N,N*-diethyl-9*H*-xanthene-3-carboxamidine (Cpd 9). A mixture of compound **5e** (0.06 g, 0.146 mmol), diethylamine (0.766 mL, 7.31 mmol) and Cu(I)Cl (0.0724 g, 0.731 mmol) in MeOH (1 mL) were exposed to microwave irradition (300 W) at 140°C for 20 min. A portion of K_2CO_3 (0.2 g, 1.45 mmol) was added to the reaction mixture and stirred at room temperature for 3 h. The solid was collected by vacuum filtration, and the crude product was purified by reverse phase HPLC to give compound **9** as a TFA salt. MS *m/z* (MH^+)387.9; ^1H NMR (CH_3OH-d_4) δ 1.22 (t, 3H), 1.39 (t, 3H), 1.48 (d, 2H), 1.96 (m, 2H), 3.12 (m, 4H), 3.42 (q, 2H), 3.7 (q, 2H), 4.07 (m, 2H), 7.28 (m, 2H), 7.40 (m, 3H), 7.53 (d, 1H), 7.61 (d, 1H).

Example 11



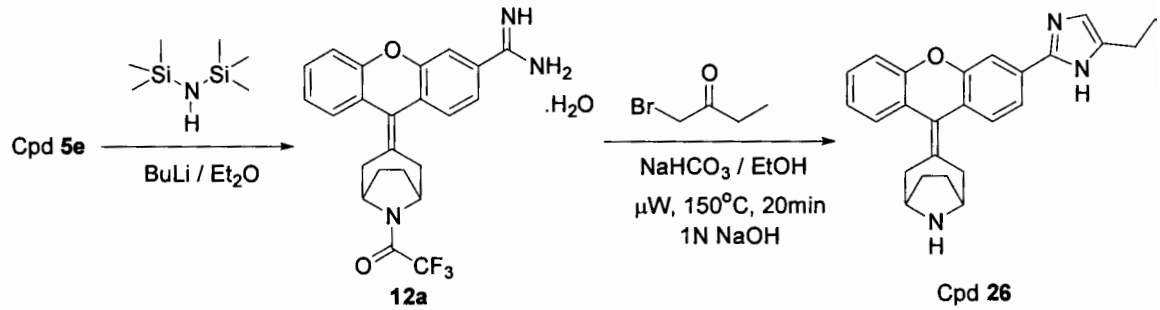
Procedure T

Acetic hydrazide benzenesulfonic acid (11a). To a solution of acetic hydrazide (2g, 27.0 mmol) in EtOH (5 mL) was added benzenesulfonic acid (4.7g, 29.7 mmol) in small portions. A white solid formed. A volume of Et_2O (5 mL) was added to the mixture. The resulting solid was collected by filtration, washed with Et_2O, and dried to give compound **11a**. ^1H NMR (D_2O) δ 1.95 (s, 3H), 7.45 (m, 3H), 7.75 (d, 2H).

Procedure U

3-[3-(5-Methyl-4H-[1,2,4]triazol-3-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]octane (35). A mixture of compounds **11a** (0.029 g, 0.125 mmol) and **5e** (0.051g, 0.124 mmol) was exposed to microwave irradition (300 W) at 200°C for 10 min. After cooling, MeOH (1 mL) and 1N NaOH (1 mL) were added to the reaction mixture and the mixture was stirred at rt for 30 min. The crude product was purified by reverse phase HPLC to yield compound **35** as a TFA salt. MS *m/z* (MH^+) 371.0; ^1H NMR (CH_3OH-d_4) δ 1.40 (d, 2H), 1.85 (m, 2H), 1.41 (s, 3H), 3.02 (m, 4H), 3.91 (m, 2H), 7.19 (m, 4H), 7.33 (d, 2H), 7.84 (d, 1H), 7.85 (s, 1H).

Example 12



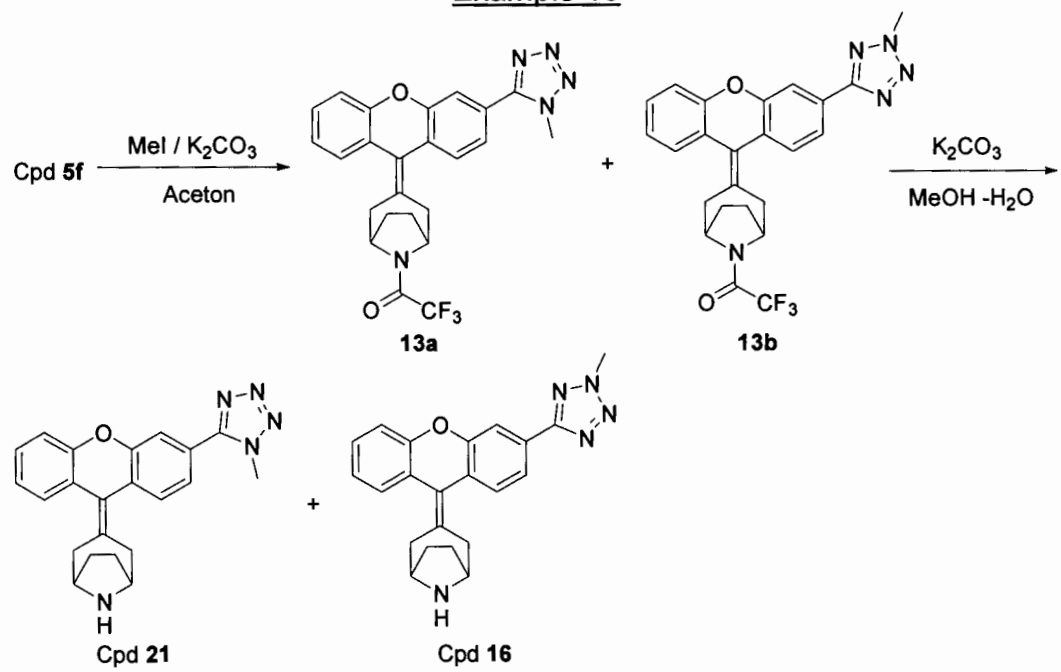
Procedure V

9-[8-(2,2,2-Trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-xanthene-3-carboxamidine (12a). To a solution of n-BuLi (2.5M in hexanes, 0.487 mL, 1.22 mmol) in Et_2O (1 mL) was added dropwise a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.257 mL, 1.22 mmol) in Et_2O (1 mL) at 0°C. The mixture was stirred at 0°C for 30 min. Compound **5e** (0.2g, 0.49 mmol) was added to the mixture and the mixture was stirred at rt for 2 h. The mixture was poured into ice-cold 2N HCl (2 mL) and extracted with Et_2O (2 x 3 mL). The aqueous phase was adjusted to pH ~8 with 1N NaOH and extracted with CH_2Cl_2 (2 x 3 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The resultant compound **12a** was used in the next reaction without further purification. MS *m/z* (MH^+) 427.8.

Procedure W

3-[3-(5-Ethyl-1*H*-imidazol-2-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]-octane (Cpd 26). A mixture of compound **12a** (0.050 g, 0.112 mmol), 1-bromo-2-butanone (0.012g, 0.118 mmol) and $NaHCO_3$ (0.02g, 0.238 mmol) in EtOH (1 mL) were exposed to microwave irradition (300 W) at 150°C for 20 min. After cooling, 1N NaOH (0.5 mL) was added to the reaction mixture and the mixture stirred at rt for 30 min. The crude product was purified by reverse phase HPLC to yield compound **26** as a TFA salt. MS *m/z* (MH^+) 384.0; ^1H NMR (CH_3OH-d_4) δ 1.39 (m, 3H), 1.52 (m, 2H), 1.96 (m, 2H), 2.83 (q, 2H), 3.15 (m, 4H), 4.09 (m, 2H), 7.30 (m, 2H), 7.43 (m, 3H), 7.63 (m, 1H), 7.72 (m, 1H), 7.85 (m, 1H).

Example 13



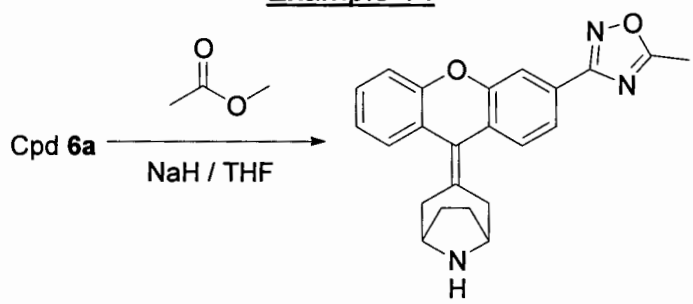
Procedure X

2,2,2-Trifluoro-1-{3-[3-(1-methyl-1H-tetrazol-5-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]oct-8-yl}-ethanone (13a) and 2,2,2-Trifluoro-1-{3-[3-(2-methyl-2H-tetrazol-5-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]oct-8-yl}-ethanone (13b). A mixture of compound **5f** (0.16g, 0.35 mmol), methyl iodide (0.044 mL, 0.71 mmol) and potassium carbonate (0.24g, 1.74 mmol) in acetone (8 mL) was heated to reflux (oil bath, 60°C) for 2 h. The mixture was allowed to cool to rt, and the solid was removed via filtration. The solvent was removed in vacuo. The mixture of crude products **13a** and **13b** was used in the next reaction without further purification. MS *m/z* (MH^+) 467.9.

3-[3-(1-Methyl-1*H*-tetrazol-5-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]octane (Cpd 21) and **3-[3-(2-Methyl-2*H*-tetrazol-5-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]octane (Cpd 16).** Using an adaptation of the method described in Procedure N and substituting the mixture of compounds **13a** and **13b** for compound **5f**, a mixture of the title compounds **21** and **16** were prepared. Compounds **21** and **16** were separated and purified via reverse phase HPLC as their TFA salts. **Cpd 21:** MS *m/z* (MH^+) 371.9; ^1H NMR

(CH_3OH-d_4,) δ 1.52 (d, 2H), 1.97 (m, 2H), 3.15 (m, 4H), 4.08 (m, 2H), 4.27 (s, 3H), 7.29 (m, 2H), 7.41 (m, 2H), 7.67 (m, 2H), 7.76 (d, 1H). **Cpd 16:** MS *m/z* (MH^+) 371.9; ^1H NMR (CH_3OH-d_4,) δ 1.52 (d, 2H), 1.95 (m, 2H), 3.12 (m, 4H), 4.06 (m, 2H), 4.45 (s, 3H), 7.24 (m, 2H), 7.37 (m, 2H), 7.53 (d, 1H), 7.96 (m, 2H).

Example 14

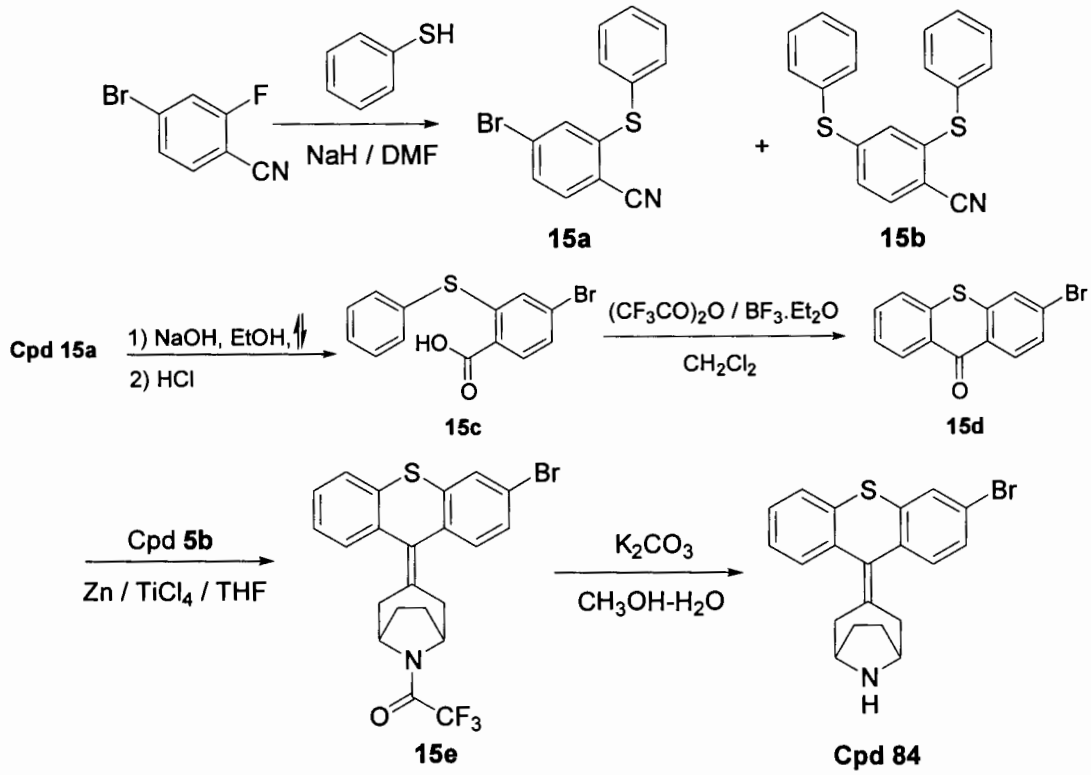


Cpd 36

Procedure Y

3-[3-(5-Methyl-[1,2,4]oxadiazol-3-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]octane (Cpd 36). A mixture of Compound **6a** (0.046g, 0.104 mmol) and NaH (60% in oil, 0.0042 mg, 0.105 mmol) in THF (4 mL) was refluxed for 1 h. After cooling, acetic acid methyl ester (0.0082 mL, 0.103 mmol) was added to the mixture. The mixture was stirred at reflux temperature overnight. The mixture was poured into ice-cold water and extracted with CH_2Cl_2 (2 x 5 mL). The organic phase was washed with H_2O, dried over $MgSO_4$, and concentrated. The crude product was purified by reverse phase HPLC to give Compound **36** as a TFA salt. MS *m/z* (MH^+) 371.9; ^1H NMR (CH_3OH-d_4,) δ 1.52 (d, 2H), 1.95 (m, 2H), 2.66 (s, 3H), 3.12 (m, 4H), 4.05 (m, 2H), 7.23 (m, 1H), 7.31 (m, 1H), 7.39 (m,2H), 7.52 (d, 1H), 7.83 (d, 1H), 7.84 (s, 1H).

Example 15



4-Bromo-2-phenylsulfanyl-benzonitrile (15a) and **2,4-Bis-phenylsulfanyl-benzonitrile (15b).** Using the method described in Procedure I, substituting benzenethiol for phenol, a mixture of the title compounds **15a** and **15b** were prepared. The mixture was separated via normal phase chromatography (eluent gradient: 0 to 20% EtOAc in heptane) to yield Compounds **15a** and **15b**. Compound **15a**: MS *m/z* (MH^+) 291.8; Compound **15b**: MS *m/z* (MH^+) 319.8.

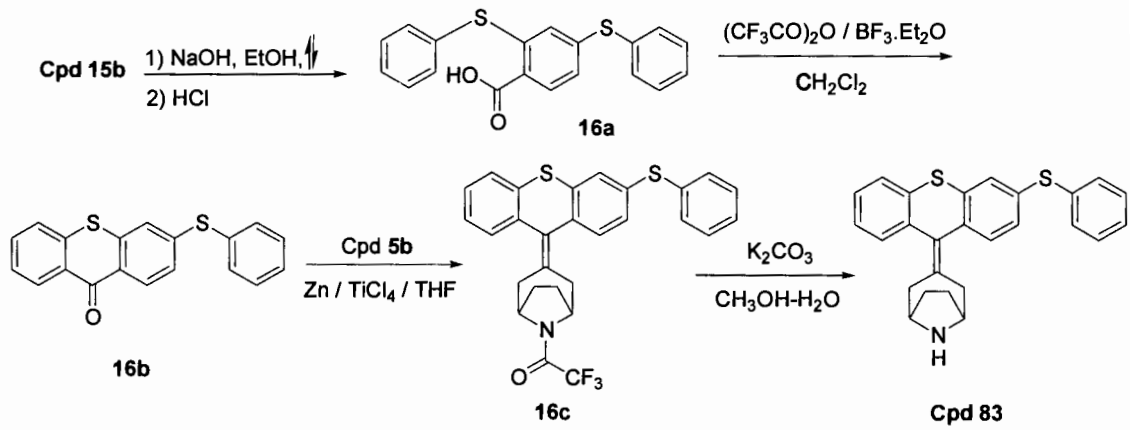
4-Bromo-2-phenylsulfanyl-benzoic acid (15c). Using the method described in Procedure J, substituting Compound **15a** for Compound **5c**, Compound **15c** was prepared. MS *m/z* (MH^+) 308.7.

3-Bromo-thioxanthen-9-one (15d). Using the method described in Procedure K, substituting Compound **15c** for Compound **1b**, Compound **15d** was prepared. MS *m/z* (MH^+) 290.7.

1-[3-(3-Bromo-thioxanthen-9-ylidene)-8-aza-bicyclo[3.2.1]oct-8-yl]-2,2,2-trifluoro-ethanone (15e). Using the method described in Procedure D, substituting Compound **15d** for *N*-[2-(9-oxo-9*H*-xanthen-3-yl)-phenyl]-acetamide and substituting Compound **5b** for 3-oxo-8-aza-bicyclo-[3.2.1] carboxylic acid tert-butyl ester, Compound **15e** was prepared. MS *m/z* (MH^+) 481.6.

3-(3-Bromo-thioxanthen-9-ylidene)-8-aza-bicyclo[3.2.1]octane (84). Using the method described in Procedure N, substituting Compound **15e** for Compound **5f**, the title compound **84** was prepared as a TFA salt. MS *m/z* (MH^+) 385.6; ^1H NMR (DMSO-d_6,) δ 1.27 (m, 2H), 1.77 (m, 2H), 2.97 (m, 4H), 4.00 (m, 2H), 7.36 (m, 4H), 7.63 (d, 1H), 7.91 (m, 3H), 8.82 (m, 1H), 9.17 (m, 1H).

Example 16



3-(3-Phenylsulfanyl-thioxanthen-9-ylidene)-8-aza-bicyclo[3.2.1]octane (16a). Using the method described in Procedure J, substituting Compound **15b** for Compound **5c**, the title compound **16a** was prepared. MS m/z (MH^+) 338.7.

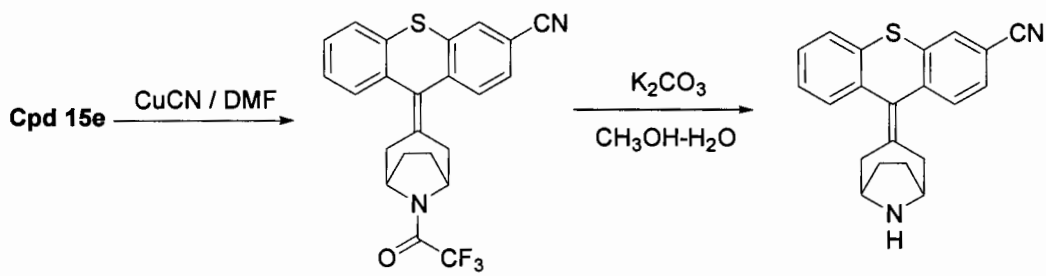
3-Phenylsulfanyl-thioxanthen-9-one (16b). Using the method described in Procedure K, substituting Compound **16a** for Compound **1b**, Compound **16b** was prepared. MS *m/z* (MH^+) 320.9.

2,2,2-Trifluoro-1-[3-(3-phenylsulfanyl-thioxanthen-9-ylidene)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethanone (16c). Using the method described in Procedure D, substituting Compound **16b** for *N*-[2-(9-oxo-9*H*-xanthen-3-yl)-phenyl]-acetamide and substituting Compound **5b** for 3-oxo-8-aza-bicyclo-[3.2.1] carboxylic acid tert-butyl ester, Compound **16c** was prepared. MS *m/z* (MH^+) 509.7.

3-(3-Phenylsulfanyl-thioxanthen-9-ylidene)-8-aza-bicyclo[3.2.1]octane (83).

Using the method described in Procedure N, substituting Compound **16c** for Compound **5f**, the title compound **83** was prepared as a TFA salt. MS *m/z* (MH^+) 413.7; ^1H NMR (CH_3OH-d_4,) δ 1.32 (m, 2H), 1.76 (m, 2H), 2.74 (m, 4H), 3.84 (m, 2H), 7.25 (m, 11H), 7.41 (d, 1H).

Example 17

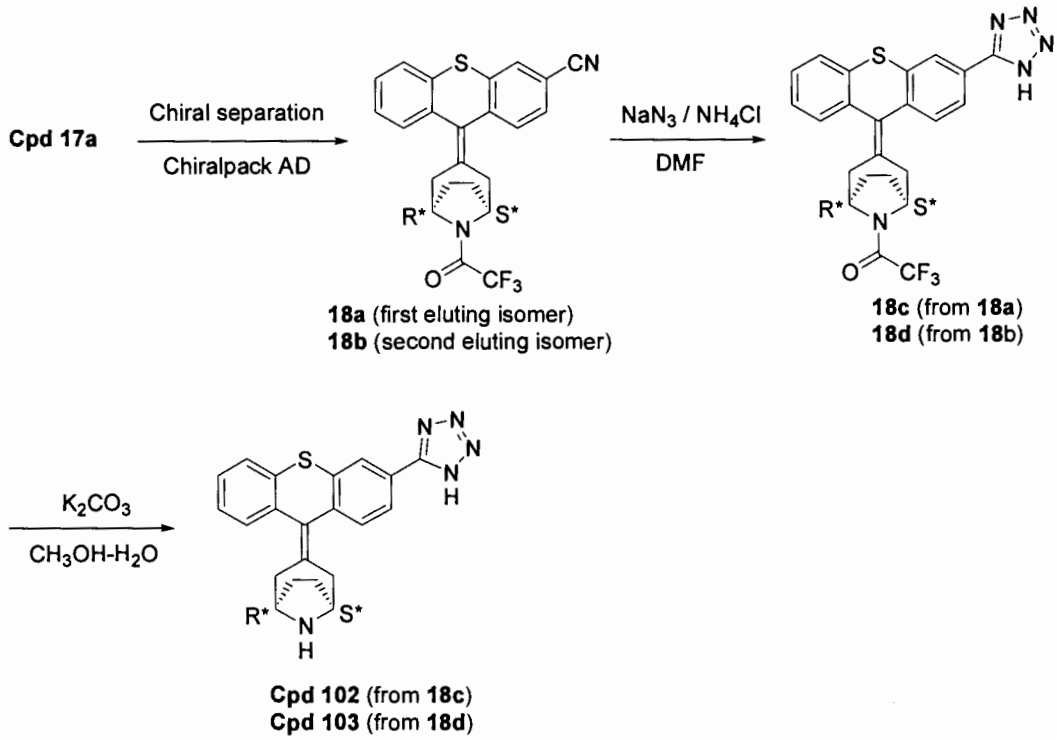


9-[8-(2,2,2-Trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-thioxanthene-3-carbonitrile (17a). Using the method described in Procedure L, substituting Compound **15e** for Compound **5d**, the title compound **17a** was prepared. MS *m/z* (MH^+) 426.7; ^1H NMR ($CDCl_3$) δ 1.41 (m, 2H), 1.83 (m, 2H), 2.76 (m, 4H), 4.40 (m, 1H), 4.70 (m, 1H), 7.33 (m, 4H), 7.56 (m, 2H), 7.51 (s, 1H).

9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-9*H*-thioxanthene-3-carbonitrile (85). Using the method described in Procedure N, substituting Compound **17a** for

Compound **5f**, the title compound **85** was prepared. MS *m/z* (MH^+) 330.9; ^1H NMR (CH_3OH-d_4) δ 1.33 (m, 2H), 1.81 (m, 2H), 2.78 (m, 4H), 3.91 (m, 2H), 7.21 (m, 3H), 7.38 (d, 1H), 7.49 (d, 1H), 7.57 (dd, 1H), 7.85 (d, 1H).

Example 18



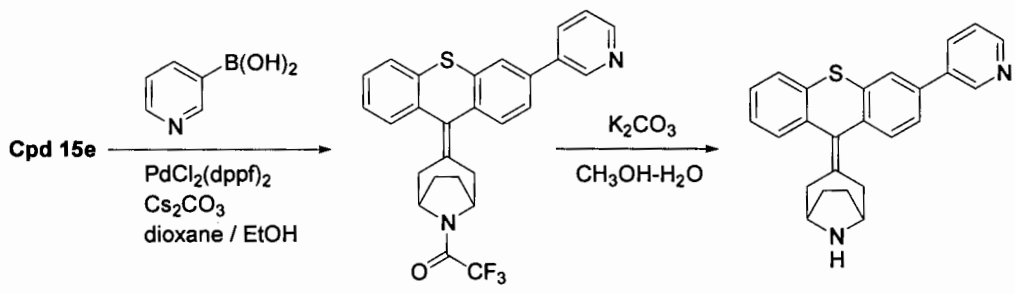
9-[(1RS,5SR)-8-(2,2,2-Trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-thioxanthene-3-carbonitrile (18a) and 9-[(1SR,5RS)-8-(2,2,2-trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-thioxanthene-3-carbonitrile (18b). Racemic Compound **17a** was separated via chiral chromatography into its enantiomers using a Chiralpack AD column (500g) and a 1:1 heptane:ethanol eluent mixture (UV monitoring at 220 nm and flow rate of 80 mL/min), yielding Compounds **18a** (first eluting isomer) and **18b** (second eluting isomer).

2,2,2-Trifluoro-1-{3-[3-(1*H*-tetrazol-5-yl)-thioxanthen-9-ylidene]-[(1RS,5SR)-8-aza-bicyclo[3.2.1]oct-8-yl}]-ethanone (18c) and 2,2,2-trifluoro-1-{3-[3-

(1*H*-tetrazol-5-yl)-thioxanthen-9-ylidene]-[(1SR,5RS)-8-aza-bicyclo[3.2.1]oct-8-yl}-ethanone (18d). Using the method described in Procedure M, substituting Compound **18a** for Compound **5e**, the title compound **18c** was prepared. MS *m/z* (MH^+) 469.8. Similarly, using the method described in Procedure M, substituting Compound **18b** for Compound **5e**, the title compound **18d** was prepared.

(1RS,5SR)-3-[3-(1*H*-Tetrazol-5-yl)-thioxanthen-9-ylidene]-8-aza-bicyclo[3.2.1]octane (Cpd 102) and (1SR,5RS)-3-[3-(1*H*-tetrazol-5-yl)-thioxanthen-9-ylidene]-8-aza-bicyclo[3.2.1]octane (Cpd 103). Using the method described in Procedure N, substituting Compound **18c** for Compound **5f**, the title compound **102** was prepared as a TFA salt. MS *m/z* (MH^+) 373.8; ^1H NMR (CH_3OH-d_4) δ 1.37 (m, 2H), 1.79 (m, 2H), 2.84 (m, 4H), 3.89 (m, 2H), 7.25 (m, 3H), 7.43 (d, 1H), 7.50 (d, 1H), 7.91 (dd, 1H), 8.13 (d, 1H). Similarly, using the method described in Procedure N, substituting Compound **18d** for Compound **5f**, the title compound **103** was prepared as a TFA salt.

Example 19



Procedure Z

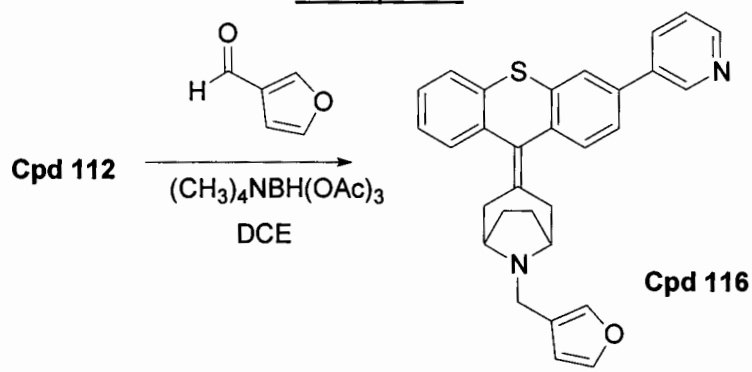
2,2,2-Trifluoro-1-[3-(3-pyridin-3-yl-thioxanthen-9-ylidene)-8-aza-bicyclo[3.2.1]oct-8-yl]-ethanone (19a)

To a suspension of compound **15e** (0.3g, 0.625 mmol), cesium carbonate (0.51g, 1.565 mmol) and 3-pyridineboronic acid (0.0844g, 0.687 mmol) in dioxane (4 mL) and EtOH (1 mL) was added 1,1'-bis-(diphenylphosphino)-

ferrocene-palladium (II) dichloride (46 mg, 0.063 mmol). The mixture was heated at 90 °C for 3 hrs, and cooled to room temperature. The solid was filtreted, and washed with CH_3OH (10mL) and H_2O (10mL). The filtrate was concentrated under reduce pressure to afford crude product. The crude product **19a** was used in the next reaction without further purification. MS *m/z* (MH^+) 479.0.

3-(3-Pyridin-3-yl-thioxanthen-9-ylidene)-8-aza-bicyclo[3.2.1]octane (Cpd 112). Using the method described in Procedure N, substituting Compound **19a** for Compound **5f**, the title compound **112** was prepared as a TFA salt. MS *m/z* (MH^+) 383.3; ^1H NMR ($CDCl_3$) δ 1.50 (m, 2H), 2.02 (m, 2H), 2.80 (t, 2H), 3.12 (m, 2H), 4.00 (m, 2H), 7.31 (m, 3H), 7.42 (d, 2H), 7.55 (dd, 1H), 7.78 (s, 1H), 7.92 (dd, 1H), 8.40 (d, 1H), 8.76 (d, 1H), 9.08 (s, 1H).

Example 20

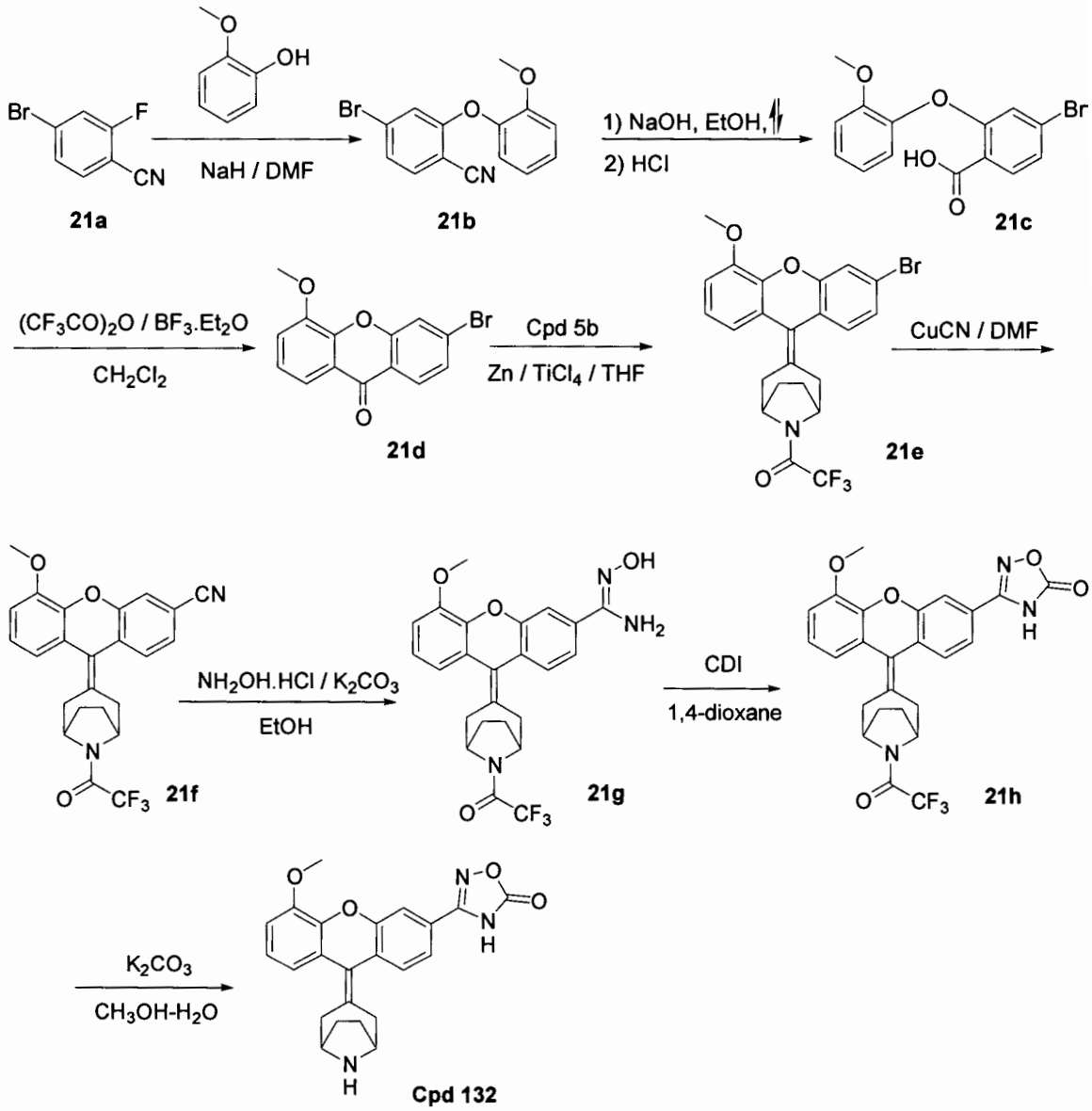


Procedure AA

8-Furan-3-ylmethyl-3-(3-pyridin-3-yl-thioxanthen-9-ylidene)-8-aza-bicyclo[3.2.1]octane (116) A mixture of compound **112** (20mg, 0.04 mmol), 3-furaldehyde (13.5mg, 0.156 mmol) and tetramethylammonium triacetoxyborohydride (16mg, 0.061 mmol) in dichloroethane (2 mL) was stirred at 80 °C overnight in a sealed tube. The solvent was removed under reduced prossure. The crude product was purified by reverse phase HPLC to give compound **116** as a TFA salt. MS *m/z* (MH^+) 463.2; ^1H NMR (CD_3CN) δ 1.45 (d, 2H), 2.06 (m, 2H), 2.90 (m, 2H), 3.80 (m, 2H), 3.98 (m, 2H), 6.69 (s, 1H),

7.35 (m, 3H), 7.48 (d, 1H), 7.61 (m, 4H), 7.78 (m, 1H), 7.96 (s, 1H), 8.41 (d, 1H), 8.75 (d, 1H), 9.01 (s, 1H).

Example 21



4-Bromo-2-(2-methoxy-phenoxy)-benzonitrile (21b). Using the method described in Procedure I, substituting 2-methoxyphenol for phenol, the title compound **21b** was prepared. MS *m/z* (MH^+) 303.8, 305.8.

4-Bromo-2-(2-methoxy-phenoxy)-benzoic acid (21c). Using the method described in Procedure J, substituting Compound **21b** for Compound **5c**, the title compound **21c** was prepared. MS *m/z* (MH^+) 322.8, 324.7.

3-Bromo-5-methoxy-xanthen-9-one (21d). Using the method described in Procedure K, substituting Compound **21c** for Compound **1b**, the title compound **21d** was prepared. MS *m/z* (MH^+) 304.8, 306.7.

1-[3-(3-Bromo-5-methoxy-xanthen-9-ylidene)-8-aza-bicyclo[3.2.1]oct-8-yl]-2,2,2-trifluoro-ethanone (21e). Using the method described in Procedure D, substituting Compound **21d** for Compound **1c** and substituting Compound **5b** for 3-oxo-8-aza-bicyclo[3.2.1]-octane-8-carboxylic acid tert-butyl ester, the title compound **21e** was prepared. MS *m/z* (MH^+) 467.7, 469.7.

5-Methoxy-9-[8-(2,2,2-trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9H-xanthene-3-carbonitrile (21f). Using the method described in Procedure L, substituting Compound **21e** for Compound **5d**, the title compound **21e** was prepared. MS *m/z* (M+23) 462.7.

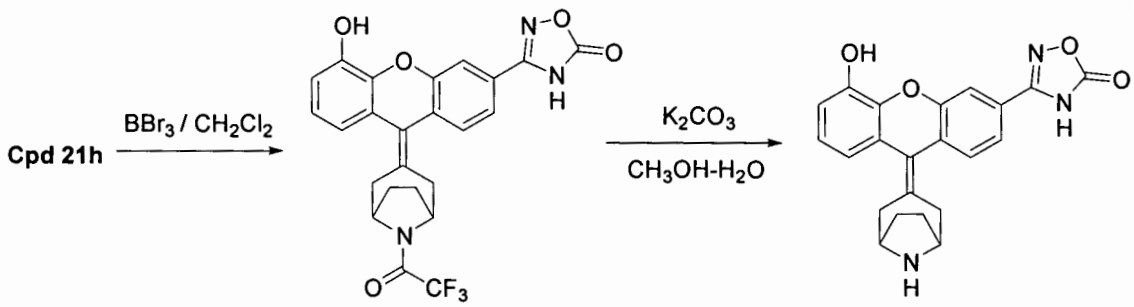
3-[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-5-methoxy-9H-xanthen-3-yl]-4H-[1,2,4]oxadiazol-5-one (21g). Using the method described in Procedure O, substituting Compound **21f** for Compound **5e**, the title compound **21g** was prepared. MS *m/z* (MH^+) 473.9.

3-{5-Methoxy-9-[8-(2,2,2-trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9H-xanthen-3-yl}-4H-[1,2,4]oxadiazol-5-one (21h). Using the method described in Procedure P, substituting Compound **21g** for Compound **6a**, the title compound **21h** was prepared. MS *m/z* (MH^+) 499.8.

3-[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-5-methoxy-9H-xanthen-3-yl]-4H-[1,2,4]oxadiazol-5-one (132). Using the method described in Procedure N, substituting Compound **21h** for Compound **5f**, the title compound **132** was

prepared as a TFA salt. MS *m/z* (MH^+) 403.9; ^1H NMR (DMSO-d_6) δ 1.28 (m, 2H), 1.79 (m, 2H), 2.98 (m, 4H), 3.90 (s, 3H), 4.03 (m, 2H), 6.98 (d, 1H), 7.10 (d, 1H), 7.19 (t, 1H), 7.65 (m, 2H), 7.74 (s, 1H).

Example 22

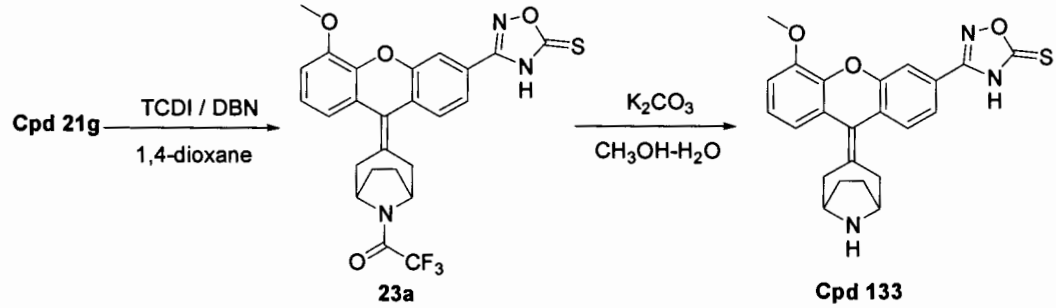


Procedure BB

3-{5-Hydroxy-9-[8-(2,2,2-trifluoro-acetyl)-8-aza-bicyclo[3.2.1]oct-3-ylidene]-9*H*-xanthen-3-yl}-4*H*-[1,2,4]oxadiazol-5-one (22a). To a solution of Compound **21h** (0.355g, 1.19 mmol) in CH_2Cl_2 (30 mL) was added dropwise BBr_3 (1.0M in CH_2Cl_2, 5.97 mL, 5.97 mmol) at 0 °C. The mixture was stirred at rt for 24h, and quenched with a saturated $NaHCO_3$ solution (20 mL). The organic layer was dried over $MgSO_4$ and concentrated. The crude product was used in the next reaction without further purification. MS *m/z* (MH^+) 485.8.

3-[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-5-hydroxy-9*H*-xanthen-3-yl]-4*H*-[1,2,4]oxadiazol-5-one (134). Using the method described in Procedure N, substituting Compound **22a** for Compound **5f**, the title compound **134** was prepared as a TFA salt. MS *m/z* (MH^+) 389.9; ^1H NMR (CH_3OH-d_4) δ 1.43 (m, 2H), 1.82 (m, 2H), 2.95 (m, 2H), 3.22 (t, 2H), 3.94 (m, 2H), 6.75 (m, 2H), 7.00 (t, 1H), 7.42 (d, 1H), 7.51 (dd, 1H), 7.65 (s, 1H).

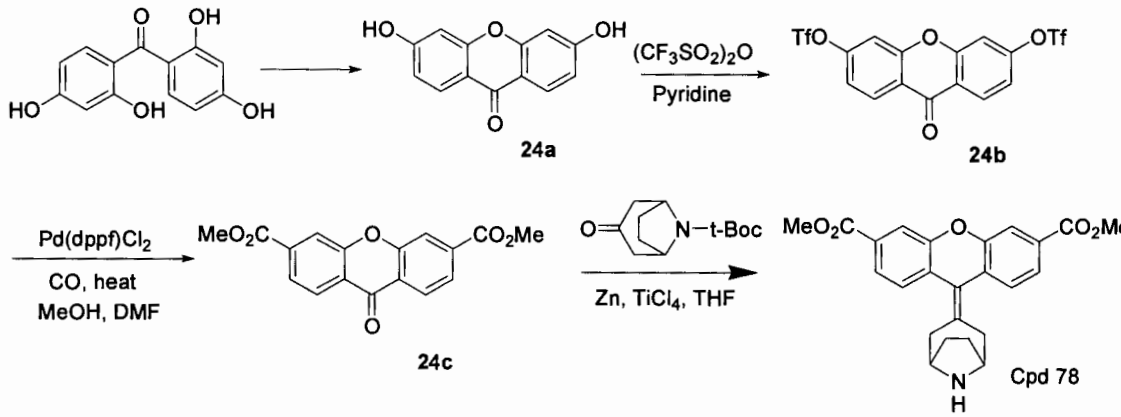
Example 23



2,2,2-Trifluoro-1-{3-[5-methoxy-3-(5-thioxo-4,5-dihydro-[1,2,4]oxadiazol-3-yl)-xanthen-9-ylidene]-8-aza-bicyclo[3.2.1]oct-8-yl}-ethanone (23a) Using the method described in Procedure P, substituting Compound **21g** for Compound **6a**, substituting 1,1'-thiocarbonyldiimidazole (TCDI) for CDI and adding 1,8-diazabicyclo[5.4.0]undec-7-ene (DBN, 1 equivalent), the title compound **23a** was prepared. MS *m/z* (MH^+) 515.8.

3-[9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-5-methoxy-9H-xanthen-3-yl]-4H-[1,2,4]oxadiazole-5-thione (133). Using the method described in Procedure N, substituting Compound **23a** for Compound **5f**, the title compound **133** was prepared as a TFA salt. MS *m/z* (MH^+) 419.9; ^1H NMR (DMSO-d_6) δ 1.26 (m, 2H), 1.78 (m, 2H), 2.93 (m, 2H), 3.32 (t, 2H), 3.90 (s, 3H), 4.00 (m, 2H), 6.98 (t, 1H), 7.10 (t, 1H), 7.28 (t, 1H), 7.58 (d, 1H), 7.81 (d, 1H), 7.90 (s, 1H).

Example 24



Procedure CC

3,6-Dihydroxy-xanthen-9-one (24a). Following a procedure disclosed in the literature, (Janjic, N. et al. *J. Am. Chem. Soc.* 1989, 111, 6374-6375) compound 24a was prepared. MS *m/z* (MH^+) 228.9.

Procedure DD

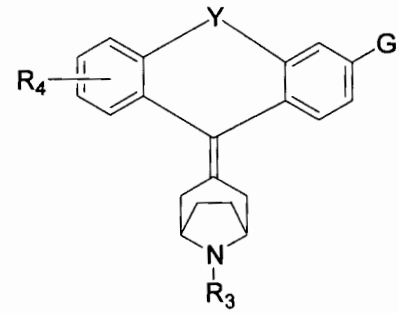
Trifluoro-methanesulfonic acid 9-oxo-6-trifluoromethane-sulfonyloxy-9*H*-xanthen-3-yl ester (24b). Compound **24a** (1.18 g, 5.18 mmol) was suspended in 30 mL of dichloromethane, treated with pyridine (836 mL), and stirred at rt for 10 min. Upon cooling to 0°C, triflic anhydride (1.73 mL, 10.3 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h and then allowed to warm to rt with additional stirring overnight. Upon completion of the reaction the mixture was concentrated under reduced pressure. The resultant residue was purified by normal phase chromatography using dichloromethane as eluant to give compound **24b**. MS *m/z* (MH^+) 492.6.

Procedure EE

9-Oxo-9H-xanthene-3,6-dicarboxylic acid dimethyl ester (24c). Compound **24b** (0.52 g, 1.06 mmol) and DIEA (553 μL) were added to a mixture of DMF:MeOH (1:1, 20 mL total volume) and the flask was purged with Argon gas. The mixture was then treated with $Pd(dppf)Cl_2$ (43 mg, 0.053 mmol), purged, then charged with carbon monoxide and heated to 75°C for 8 h. The mixture was cooled to rt and concentrated under reduced pressure at 50°C. The resultant residue was taken up in CH_2Cl_2, and washed sequentially with 1 N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was partitioned, dried over magnesium sulfate, filtered, and the filtrate was concentrated to a residue. The residue was purified by normal phase chromatography using a gradient of 0.1 to 0.4 % MeOH in dichloromethane as eluant to give compound **24c**.

9-(8-Aza-bicyclo[3.2.1]oct-3-ylidene)-9*H*-xanthene-3,6-dicarboxylic acid dimethyl ester (78). The title compound was prepared according to Procedure D, substituting 9-oxo-9H-xanthene-3,6-dicarboxylic acid dimethyl ester for *N*-[2-(9-oxo-9H-xanthen-3-yl)-phenyl]-acetamide.

Compounds 1 through 134 of Formula (Ia) (wherein R_5 is H and A is CH_2CH_2), in the table below were synthesized using the procedures described above.



Formula (Ia)

Cpd	G	R_3	R_4	Y
1	1*H*-tetrazol-5-yl	H	H	O
2	2-methylcarbonyl aminophenyl	H	H	O
3	*N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl	ethoxy carbonyl	H	O
4	4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl	H	H	O
5	4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl	H	H	O
6	pyrrolidin-1-ylcarbonyl	H	H	O
7	*N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl	H	H	O
8	4*H*-[1,2,4]thiadiazol-5-oxo-3-yl	H	H	O
9	*N,N*-diethylamidino	H	H	O
10	[1,2,3,5]oxathiadiazol-2-oxo-4-yl	H	H	O

Cpd	G	R_3	R_4	Y
11	*N*-(3-fluorophenyl)-methyl-aminocarbonyl	H	H	O
12	pyridin-3-yl	H	H	O
13	*N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl] aminocarbonyl	H	H	O
14	*N*-phenyl-*N*-methyl-aminocarbonyl	H	H	O
15	*N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl	H	H	O
16	2-methyl-tetrazol-5-yl	H	H	O
17	*N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl	H	H	O
18	2-aminocarbonyl-phenyl	H	H	O
19	2-phenylethyl-aminocarbonyl	H	H	O
20	3-methylcarbonylamino-phenyl	H	H	O
21	1-methyl-tetrazol-5-yl	H	H	O
22	*N*-cyclohexyl-*N*-methyl-aminocarbonyl	H	H	O
23	3-hydroxymethyl-phenyl	H	H	O
24	*N*-hydroxyamidino	H	H	O
25	2-aminophenyl	H	H	O

Cpd	G	R_3	R_4	Y
26	5-ethyl-1*H*-imidazol-2-yl	H	H	O
27	*N*-(1(*R*)-hydroxymethyl-2-phenyl-eth-1-yl)-aminocarbonyl	H	H	O
28	*N, N*-diisobutylamidino	H	H	O
29	pyridin-4-yl	H	H	O
30	4-methylcarbonylamino-phenyl	H	H	O
31	*N*-(1*S*-methoxymethyl-2-phenyl-eth-1-yl)aminocarbonyl	H	H	O
32	2-methoxypyridin-5-yl	H	H	O
33	4,5-dihydro-1*H*-imidazol-2-yl	H	H	O
34	*N*-(4-phenyl)-cyclohexyl-aminocarbonyl	H	H	O
35	3-methyl-4*H*-[1,2,4] triazol-5-yl	H	H	O
36	5-methyl-[1,2,4] oxadiazol-4-yl	H	H	O
37	*N*-(1(*S*)-hydroxymethyl-1-methoxycarbonyl)amino carbonyl	H	H	O
38	3-hydroxy-phenyl	H	H	O
39	isopropylamidino	H	H	O
40	phenylmethylamino carbonyl	H	H	O

Cpd	G	R_3	R_4	Y
41	1,4,5,6-tetrahydro pyrimidin-2-yl	H	H	O
42	4-aminophenyl	H	H	O
43	*C*-piperidin-1-yl-methyleneamine	H	H	O
44	2-methoxyphenyl	H	H	O
45	cyclopentylaminocarbonyl	H	H	O
46	3-methylphenyl	H	H	O
47	phenylaminocarbonyl	H	H	O
48	*N,N*- bis (2,2,2-trifluoro-eth-1-yl)aminocarbonyl	H	H	O
49	isobutylamidino	H	H	O
50	*C*-morpholin-4-yl-methyleneamine	H	H	O
51	3-fluorophenyl	H	H	O
52	*N*-benzyl-*N*-methyl-aminocarbonyl	H	H	O
53	4-methanesulfonyl-phenyl	H	H	O
54	4-fluorophenyl	H	H	O
55	thiophen-3-yl	H	H	O
56	*N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl	H	H	O

Cpd	G	R_3	R_4	Y
57	3-methoxyphenyl	H	H	O
58	phenylmethylamino carbonyl	ethoxy carbonyl	H	O
59	phenylaminocarbonyl	ethoxy carbonyl	H	O
60	cyclopentylaminocarbonyl	ethoxy carbonyl	H	O
61	*N*-(2-hydroxy-ethyl)-*N*-methyl-aminocarbonyl	H	H	O
62	*N*-[(4-trifluoromethyl)-cyclohexyl]-aminocarbonyl	H	H	O
63	3-methanesulfonylamino-phenyl	H	H	O
64	*N*-2,2,2,-trifluoroethyl-aminocarbonyl	H	H	O
65	3-[(3-methoxy)phenyl]piperidin-1-ylcarbonyl	H	H	O
66	*N*-4-fluorophenyl-*N*-methyl-aminocarbonyl	H	H	O
67	*N*-(1(*R*)-hydroxymethyl-3-methyl-but-1-yl)-aminocarbonyl	H	H	O
68	*N*-(dimethylamino carbonylmethyl)-*N*-methyl-aminocarbonyl	H	H	O
69	(3(*R*)-hydroxy) pyrrolidin-1-ylcarbonyl	H	H	O
70	(3(*S*)-hydroxy) pyrrolidin-1-ylcarbonyl	H	H	O
71	pyridin-3-yl	H	5-methoxy	O
72	carboxy	H	H	O

Cpd	G	R_3	R_4	Y
73	methoxycarbonyl	H	H	O
74	methoxycarbonyl	ethoxy carbonyl	H	O
75	*N*-(2-hydroxy-ethyl)-*N*-methyl-aminocarbonyl	ethoxy carbonyl	H	O
76	methoxycarbonyl	H	H	S
77	cyano	H	H	O
78	methoxycarbonyl	H	6-methoxy carbonyl	O
79	bromo	H	5-methoxy	O
80	1*H*-tetrazol-5-yl	H	H	O
81	1*H*-tetrazol-5-yl	H	H	O
82	1*H*-tetrazol-5-yl	H	5-methoxy	O
83	phenylthio	H	H	S
84	bromo	H	H	S
85	cyano	H	H	S
86	cyano	H	H	O
87	cyano	H	H	O
88	cyano	trifluoro methyl carbonyl	H	O

Cpd	G	R_3	R_4	Y
89	cyano	trifluoro methyl carbonyl	H	O
90	1*H*-tetrazol-5-yl	H	5-hydroxy	O
91	4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl	H	H	O
92	4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl	H	H	O
93	4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl	H	H	O
94	4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl	H	H	O
95	4*H*-[1,2,4]thiadiazol-5-oxo-3-yl	H	H	O
96	methoxycarbonyl	H	H	O
97	*N*-(2-hydroxy-1,1-dimethyl-ethyl)-aminocarbonyl	H	H	O
98	carboxy	*t*-butoxy carbonyl	H	O
99	carboxy	H	H	O
100	carboxy	H	H	O
101	4*H*-[1,2,4]thiadiazol-5-oxo-3-yl	H	H	O
102	1*H*-tetrazol-5-yl	H	H	S
103	1*H*-tetrazol-5-yl	H	H	S
104	quinolin-3-yl	H	5-methoxy	O

Cpd	G	R_3	R_4	Y
105	fur-3-yl	H	5-methoxy	O
106	thien-3-yl	H	5-methoxy	O
107	pyridin-4-yl	H	5-methoxy	O
108	2-methylcarbonylamino-phenyl	H	5-methoxy	O
109	quinolin-3-yl	H	5-hydroxy	O
110	*N*-(2-hydroxy-ethyl)-aminocarbonyl	H	H	O
111	1-methyl-pyrazol-3-yl	H	H	O
112	pyridin-3-yl	H	H	S
113	2-methylcarbonylamino-phenyl	H	H	S
114	pyridin-3-yl	methyl	H	S
115	pyridin-3-yl	1*H*-imidazol-2-ylmethyl	H	S
116	pyridin-3-yl	fur-3-ylmethyl	H	S
117	pyridin-3-yl	pyridin-2-yl methyl	H	S
118	2-methylcarbonylamino-phenyl	methyl	H	S
119	2-methylcarbonylamino-phenyl	1*H*-imidazol-2-ylmethyl	H	S
120	2-methylcarbonylamino-phenyl	fur-3-yl methyl	H	S

Cpd	G	R_3	R_4	Y
121	2-methylcarbonylamino-phenyl	pyridin-2-yl methyl	H	S
122	*N*-(2-hydroxy-ethyl)-aminocarbonyl	*t*-butoxy carbonyl	H	O
123	*N*-(2-hydroxy-ethyl)-aminocarbonyl	H	H	O
124	*N*-(2-hydroxy-ethyl)-*N*-methyl-aminocarbonyl	H	H	O
125	*N,N*-diethylamidino	H	H	O
126	*N,N*-diethylamidino	H	H	O
127	(3(*R*)-hydroxy) pyrrolidin-1-ylcarbonyl	H	H	O
128	pyridin-3-yl	trifluoro methyl carbonyl	H	O
129	pyridin-3-yl	trifluoro methyl carbonyl	H	O
130	2-methylcarbonyl aminophenyl	trifluoro methyl carbonyl I	H	O
131	2-methylcarbonyl aminophenyl	trifluoro methyl carbonyl	H	O
132	4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl	H	5-methoxy	O
133	4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl	H	5-methoxy	O
134	4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl	H	5-hydroxy	O

Biological Examples

Example 1

Rat Brain Delta Opioid Receptor Binding Assay

Procedure: Male, Sprague Dawley rats (150-250 g, VAF, Charles River, Kingston, NY) were killed by CO_2, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains were separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains were homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate was diluted to a concentration of 1 g of forebrain tissue per 80 mL Tris and centrifuged at 39,000 x g for 10 min. The pellet was resuspended in the same volume of Tris buffer containing 5 mM $MgCl_2$ with several brief pulses from a Polytron homogenizer. This particulate preparation was used for the delta opioid binding assays. Following incubation with the delta selective peptide ligand ~4 nM [^{3}H]DPDPE at 25°C for 2.5 h in a 96-well plate with total volume of 1 mL, the plate contents 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 µL of Betaplate Scint scintillation fluid (LKB) was added and the radioactivity 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: [(total dpm-test compound dpm)/(total dpm-nonspecific dpm)]*100. Kd and Ki values were calculated using GraphPad PRISM data analysis program.

Example 2

Rat Brain Mu Opioid Receptor Binding Assay

Procedure: Male, Sprague Dawley rats (150-250 g, VAF, Charles River, Kingston, NY) were killed by CO_2, and their brains removed and placed immediately in ice cold Tris HCl buffer (50 mM, pH 7.4). The forebrains were separated from the remainder of the brain by a coronal transection, beginning dorsally at the colliculi and passing ventrally through the midbrain-pontine junction. After dissection, the forebrains were homogenized in Tris buffer in a Teflon®-glass homogenizer. The homogenate was diluted to a concentration of 1 g of forebrain tissue per 80 mL Tris and centrifuged at 39,000 x g for 10 min. The pellet was resuspended in the same volume of Tris buffer containing 5 mM $MgCl_2$ with several brief pulses from a Polytron homogenizer. This particulate preparation was used for the delta opioid binding assays. Following incubation with the mu selective peptide ligand, ~0.8 nM [^{3}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 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 µL of Betaplate Scint scintillation fluid (LKB) was added and the radioactivity quantifed 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 tested). Percent inhibition was calculated as: [(total dpm-test compound dpm)/(total dpm-nonspecific dpm)]*100. Kd and Ki values were calculated using GraphPad PRISM data analysis program.

Example 3

[^{35}S]GTPγS Binding Assay in NG108-15 Cell Membranes (delta opioid)

Methods: NG108-15 cell membranes were purchased from Applied Cell Sciences (Rockville, MD). 8 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 $MgCl_2$, 100 mM NaCl, 1 mM DTT and 1 mM EGTA. The 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 SPA (10 mg/mL) at 25°C for 45 min in the assay buffer. The SPA (5 mg/mL) coupled with membranes (37.5 µg/mL) was then incubated with 0.1 nM [^{35}S] GTPγS in the same Tris buffer containing 100 µM GDP in total volume of 200 µL. Increasing concentrations of receptor agonists were used to stimulate [^{35}S]- GTPγS binding. The basal binding was tested in the absence of agonists and non-specific binding was tested in the presence of 10 µM unlabeled GTPγS. The data were analyzed on a Packard Top Count.

DATA

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

EC_{50} value values were calculated using GraphPad Prism.

Example 4

[^{35}S]GTPγS Binding Assays in CHO-hMOR Cell Membranes

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 $MgCl_2$, 100 mM NaCl, 1 mM DTT and 1 mM EDTA. The membrane suspension was homogenized with a Polytron and centrifuged at 3,000 rpm for 10 min. The supernatant was then centrifuged at 18,000 rpm for 20 min. The pellet was resuspended in 10 mL assay buffer with a Polytron. The membranes were preincubated with wheat germ agglutinin coated SPA beads (Amersham) at 25°C for 45 min in the assay buffer. The SPA bead (5 mg/mL) coupled

membranes (10 μg/mL) were then incubated with 0.5 nM [^{35}S]GTPγS in the assay buffer. The basal binding 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 [^{35}S]GTPγS binding. Both basal and non-specific binding was tested in the absence of agonist; non-specific binding determination included 10 μM unlabeled GTPγS.

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

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

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

EC_{50} values were calculated using GraphPad Prism.

Biological and Mass Spectral Data

Cpd No.	DOR Ki (nM)	MOR Ki (nM)	DOR GTPγS EC_{50} (nM)	hMOR GTPγS EC_{50} (nM)	Parent peak obs	MS calcd
1	1.99	637	189/ 70.3		357.9	357.42
2	4.36	1136	394.0		423.2	422.53
3	10000	10000			490.4	489.62
4	6.78	768	128.0		374.0	373.41
5	6.89	1017	104.0		389.9	389.48

Cpd No.	DOR Ki (nM)	MOR Ki (nM)	DOR GTPγS EC_{50} (nM)	hMOR GTPγS EC_{50} (nM)	Parent peak obs	MS calcd
6	7.40	1396	59.0		387.2	386.49
7	7.63	1815	173.0		405.2	404.51
8	10.79	1083	359.0		389.9	389.48
9	14	3537			387.9	387.53
10	15.15	819			393.9	393.46
11	18.52	739	209.0		441.3	440.52
12	24	2132	587.0	0.47	367.1	366.46
13	23.57	2922	641.0		495.6	494.63
14	27.10	1157			423.2	422.53
15	27.48	414	79.0		467.3	466.58
16	30	1458	573.0	0.48	371.9	371.44
17	37.01	37			451.2	450.58
18	38	1537			409.2	408.50
19	44.99	438			437.4	436.55
20	46.58	2802			423.5	422.53
21	54	1743			371.9	371.44
22	54.90	1124			429.5	428.58
23	75	3507			396.4	395.50
24	76.83	621			347.9	347.42
25	77.42	1665			381.2	380.49
26	81	249			384.0	383.49

Cpd No.	DOR Ki (nM)	MOR Ki (nM)	DOR GTPγS EC_{50} (nM)	hMOR GTPγS EC_{50} (nM)	Parent peak obs	MS calcd
27	100.33	100			467.1	466.58
28	107.45	3103			444.0	443.63
29	133	1817			367.0	366.46
30	139	2738			423.3	422.53
31	142.33	660			481.5	480.61
32	160	10000			397.2	396.49
33	223.50	315			357.9	357.46
34	246.87	6237			491.5	490.65
35	266	673			371.0	370.46
36	373	3550			371.9	371.44
37	412.14	950			435.3	434.49
38	418	706			382.2	381.47
39	441.15	5169			374.0	373.50
40	456.10	3087			423.4	422.53
41	464.15	875			372.0	371.48
42	490	1314			381.2	380.49
43	496.07	5341			399.9	399.54
44	659	7583			396.1	395.50
45	673.20	3099			401.4	400.52
46	723	10000			380.1	379.50
47	812.60	1197			409.4	408.50

Cpd No.	DOR Ki (nM)	MOR Ki (nM)	DOR GTPγS EC_{50} (nM)	hMOR GTPγS EC_{50} (nM)	Parent peak obs	MS calcd
48	938.60	2061				496.45
49	1325.85	4019			388.0	387.53
50	1757.50	14910			402.0	401.51
51	2445	16470			384.4	383.47
52	2732.95	1831			437.2	436.55
53	3144	3290			444.1	443.56
54	4470	10000			384.3	383.47
55	4724	9282			372.2	371.50
56	4929.75	28456			417.9	417.55
57	6958	19660			396.1	395.50
58	10000	10000			495.3	494.59
59	10000	10000			481.1	480.56
60					473.6	472.58
61	6.25	876			391.0	390.48
62	309	7400			483.5	482.55
63	161	5120			459.4	458.58
64	52	411			415.4	414.43
65	88	317			507.5	506.65
66	93	935			441.5	440.52
67	360	1568			433.4	432.56
68	8.5	2389	5960/ 98.8		0.0	431.54

Cpd No.	DOR Ki (nM)	MOR Ki (nM)	DOR GTPγS EC_{50} (nM)	hMOR GTPγS EC_{50} (nM)	Parent peak obs	MS calcd
69	105	2060			403.4	402.49
70	63	1660			403.3	402.49
71	5.7	1145	1940.0			396.49
72	216	1960				333.39
73	1008	6345				347.41
74	---	---				419.48
75	4468	10000				462.55
76	370	4743				363.48
77	2707	2476				314.39
78	1152	7002				405.45
79	191.7	4776				398.30
80	87.1 / 1.38	7523 / 2571	226.0		357.9	357.42
81	0.5	261	183 / 17.1		357.9	357.42
82	5.6	307	88.4			387.44
83	8506	>10000			413.7	413.60
84	2899.0	>10000			258.6	384.34
85	628.6	2311			330.9	330.45
86	---	---			314.9	314.39
87	---	---			314.9	314.39
88	---	---			410.7	410.39
89	---	---			410.7	410.39

Cpd No.	DOR Ki (nM)	MOR Ki (nM)	DOR GTPγS EC_{50} (nM)	hMOR GTPγS EC_{50} (nM)	Parent peak obs	MS calcd
90	13 / 0.4	0.7 / 6.0	0.7	90		373.42
91	0.76	>10000	72.2		373.8	373.41
92	0.07	502	102.0		374	373.41
93	0.37	3744	631.0		389.9	389.48
94	0.04	219	126.0		389.9	389.48
95	159	4928			389.9	389.48
96	---	---				347.41
97	266	1895				404.51
98	---	---				433.50
99	---	---				333.39
100	---	---				333.39
101	7.0	465	281.0		389.9	389.48
102	54	2771			373.8	373.48
103	10.1	329	49.6		373.8	373.48
104	246	1713				446.55
105	88	497				385.46
106	281	2744				401.53
107	106	597				396.49
108	33.9	426	117.0			452.55
109	2.22	31	94.2	1226		432.52
110	---	---			377.2	376.46

Cpd No.	DOR Ki (nM)	MOR Ki (nM)	DOR GTPγS EC_{50} (nM)	hMOR GTPγS EC_{50} (nM)	Parent peak obs	MS calcd
111	220	2645			370.2	369.47
112	481	1011			383.3	382.53
113	90	1518			439.2	438.59
114	108	109			397.2	396.56
115	91	60			463.2	462.62
116	93	113			463.2	462.61
117	95	97			474.1	473.64
118	612	2071			453.1	452.62
119	142	349			519.3	518.68
120	54	183			519.2	518.68
121	3.7	137			530.2	529.71
122	>10000	>10000				476.57
123	106	1016				376.46
124	>10000	>10000			491.2	490.60
125	6.3	2049	78.3	>10,000	388.2	387.53
126	1414	>10000	>10,000	>10,000	388.2	387.53
127	191	907			403.2	402.49
128	>10000	>10000			463.2	462.47
129	>10000	>10000			463.2	462.47
130	>10000	>10000			519.2	518.53
131	>10000	>10000			519.2	518.53

Cpd No.	DOR Ki (nM)	MOR Ki (nM)	DOR GTPγS EC_{50} (nM)	hMOR GTPγS EC_{50} (nM)	Parent peak obs	MS calcd
132	0.32	254			403.9	403.44
133	2.37	371			419.9	419.50
134	0.12	2			389.9	389.41

DOR Ki: Rat delta opioid receptor binding constant

MOR Ki: Rat mu opioid receptor binding constant

Example 5

Rat CFA Radiant Heat model of inflammatory pain

Intraplantar injection of Complete Freund's Adjuvant (CFA) in rodents results in a strong, long-lasting inflammatory reaction, characterized by a chronic and pronounced hyperalgesia to both thermal and mechanical stimuli. These effects peak between 24-72 h following injection, and can last for several days to a few weeks. To assess the ability of compounds to reverse thermal hyperalgesia, male Sprague-Dawley rats (200-350 g) are given an intraplantar injection of CFA (1:1 CFA:saline, 100 μL) into their left hindpaw. Following a 24-h incubation period, response latencies on the Radiant Heat Paw Stimulator (RH) are obtained and compared to baseline (pre-CFA) latencies. The RH device automatically registers lifting of the paw from the surface of the glass. Only rats that exhibit at least a 25% reduction in response latency from baseline (i.e. hyperalgesia) are included in further analysis. Following the post CFA latency assessment, rats are dosed orally (2.5mL/kg) with test compound or vehicle (hydroxypropylmethylcellulose, HPMC). Percent reversal of hyperalgesia is calculated for each animal as (Treatment Response – postCFA Response) / (preCFA Response – postCFA Response) x 100. Therefore, a return to normal pre-CFA thresholds is defined as 100% efficacy, whereas no

change from post-CFA thresholds is 0% efficacy. Average % reversal of hyperalgesia is then calculated for each treatment group (n=6-8 rats/group).

Example 6

The therapeutic effect of delta opioid agonists has been demonstrated in:

Pain

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Example 7

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Cough

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Example 8

Delta, mu analgesic synergy

Delta and mu opioid agonists have been repeatedly demonstrated to produce antinociceptive synergy: (Vaught and Takemori, (1979) Journal of Pharmacology and Experimental Therapeutics 211:280-3; Vaught and Takemori, (1979) Journal of Pharmacology and Experimental Therapeutics 208:86-90; Porreca, Jiang and Tallarida, (1990) European Journal of Pharmacology 179:463-8; Sutters, Miakowski, Taiwo and Levine, (1990) Brain Research 530:290-4; Horan, Tallarida, Haaseth, Matsunaga, Hruby and Porreca, (1992) Life Sciences 50:1535-41; Malmberg and Yaksh, (1992) Journal of Pharmacology and Experimental Therapeutics 263:264-75; Adams, Tallarida, Geller and Adler, (1993) Journal of Pharmacology and Experimental Therapeutics 266:1261-7; Dykstra, Schoenbaum, Yarbrough, McNutt and Chang, (1993) Journal of Pharmacology and Experimental Therapeutics 267:875-82; Rossi, Pasternak and Bodnar, (1994) Brain Research 665:85-93; Negri, Improta, Lattanzi, Potenza, Luchetti and Melchiorri, (1995) British Journal of Pharmacology 116:2931-8; Dykstra, Granger, Allen, Zhang and Rice, (2002) Psychopharmacology (Berlin, Germany) 163:420-429).

Example 9

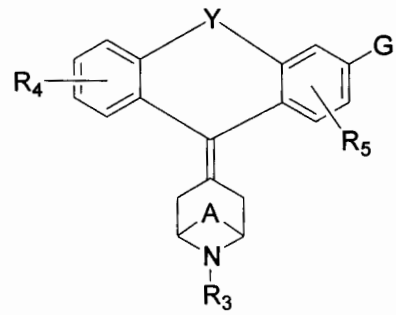
Delta, mu reduced side effect profile

Combinations of delta and mu opioid agonists have demonstrated reduced side effect profiles including fewer convulsions, lower incidence of straub tail, and attenuated respiratory depression (O'Neill, Collins, Pettit, McNutt and Chang, (1997) Journal of Pharmacology and Experimental Therapeutics 282:271-277; Su, McNutt and Chang, (1998) Journal of Pharmacology and Experimental Therapeutics 287:815-823).

Therefore compounds dually embodying delta and mu opioid pharmacologies will have greater analgesic action and a reduced side effect profile than that derived from either sole pharmacology.

Claims:

1. A compound of Formula (I):



Formula (I)

wherein:

G is $-C(Z)NR_1R_2$, C_{6-10}aryl, C_{6-10}arylthio, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, indazolyl, indolyl, indolinyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, and pyridinyl; wherein the C_{6-10}aryl group in the C_{6-10}aryl-containing substituents of G and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, nitro, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, C_{1-8}alkanylsulfonylamino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

R_1 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, and C_{2-8}alkynyl;

R_2 is a substituent selected from the group consisting of hydrogen; C_{1-8}alkanyl; C_{2-8}alkenyl; C_{2-8}alkynyl; C_{6-10}aryl; and C_{3-8}cycloalkanyl; provided that when Z is O or S, R_2 is other than

hydrogen or unsubstituted C_{1-8}alkanyl; and, wherein C_{1-8}alkanyl of R_2 is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanyloxy, C_{1-6}alkanylthio, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, C_{1-6}alkanyloxycarbonyl, and aryloxy; wherein the phenyl and aryloxy substituents of C_{1-8}alkanyl are further substituted with, and the C_{6-10}aryl and C_{3-8}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, trifluoromethyl, trifluoromethoxy, phenyl, halogen, cyano, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with one to three C_{1-4}alkanyl or C_{1-4}alkanyloxy substituents) and one to two additional substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

or, R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

R_3 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, halo$_{1-3}$(C_{1-8})alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkanyl, cycloalkanyl(C_{1-8})alkanyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, C_{1-8}alkanyloxycarbonyl, halo$_{1-3}$(C_{1-8})alkanylcarbonyl, formyl, thioformyl, carbamimidoyl,

phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, phenyl(C_{1-8})alkenyl, phenyl(C_{1-8})alkynyl, naphthyl(C_{1-8})alkanyl and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiazolyl; wherein phenyl, naphthyl, and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl, thioureido, and fluoro(C_{1-6})alkanyloxy; alternatively, when phenyl and heteroaryl are optionally substituted with alkanyl or alkanyloxy substituents attached to adjacent carbon atoms, the two substituents can together form a fused cyclic alkanyl or cycloheteroalkanyl selected from the group consisting of $-(CH_2)_{3-5}-$, $-O(CH_2)_{2-4}-$, $-(CH_2)_{2-4}O-$, and $-O(CH_2)_{1-3}O-$;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl(C_{2-6})alkynyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, aminocarbonyl, C_{1-6}alkanylaminocarbonyl, di(C_{1-6}alkanyl)aminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, mercapto, aminothiocarbonyl, amidino, hydroxyamidino, phenylcarbonyl, -C(=NOH)phenyl, aminomethyl, hydroxymethyl, methanesulfonylamino, C_{6-10}arylamino (wherein C_{6-10}aryl is optionally substituted with one to three substitutents independently selected from the group consisting of C_{1-6}alkanyl,

C_{1-6}alkoxy, halogen, and hydroxy), dihydroimidazolyl, formylamino, thioformylamino, pyridinylamino, cyano, hydroxycarbonyl, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, thienyl, fluoroalkanyl and fluoroalkanyloxy; or optionally, when R_4 is two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the fused moiety is selected from the group consisting of $-(CH_2)_{3-5}-$, $-O(CH_2)_{2-4}-$, $-(CH_2)_{2-4}O-$, $-O(CH_2)_{1-3}O-$ and $-S-C(NH_2)=N-$;

R_5 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl and fluoro(C_{1-6})alkanyloxy;

A is absent or $-(CH_2)_m-$, wherein m is 2 or 3;

Y is $-(CH_2)_nX-$ or $-X(CH_2)_n-$;

X is O or S

n is 0 or 1;

Z is O, S, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl);

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

2. The compound according to claim 1 wherein G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl,

isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, aminocarbonyl, aminothiocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino.

3. The compound according to claim 1 wherein G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group consisting of imidazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkanyl, C_{1-4}alkanyloxy, hydroxy(C_{1-4})alkanyl, carboxy(C_{1-4})alkanyl, C_{1-4}alkanylcarbonylamino, hydroxy, cyano, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, aminocarbonyl, aminothiocarbonyl, C_{1-8}alkanylaminocarbonyl, and di(C_{1-8}alkanyl)aminocarbonyl.

4. The compound according to claim 1 wherein G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group consisting of imidazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, thiophenyl, isothiazolyl, isoxazolyl, isoxadiazolyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkanyl, C_{1-4}alkanyloxy, hydroxy(C_{1-4})alkanyl, C_{1-4}alkanylcarbonylamino, hydroxy, cyano, oxo, thioxo, and aminocarbonyl.

5. The compound according to claim 1 wherein R_1 is a substituent selected from the group consisting of hydrogen and C_{1-4}alkanyl.

6. The compound according to claim 1 wherein R_1 is selected from the group consisting of hydrogen, methyl, ethyl, and propyl.

7. The compound according to claim 1 wherein R_1 is selected from the group consisting of hydrogen, methyl, and ethyl.

8. The compound according to claim 1 wherein R_2 is selected from the group consisting of hydrogen; C_{1-4}alkanyl; phenyl; and C_{3-6}cycloalkanyl; provided that when Z is O or S, R_2 is other than hydrogen or unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-4}alkanyloxy, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl and C_{3-6}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{1-8}alkanyloxy, trifluoromethyl, phenyl, fluoro, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino; or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with C_{1-4}alkanyloxy or hydroxy), C_{1-4}alkanyl, or hydroxy.

9. The compound according to claim 1 wherein R_2 is selected from the group consisting of C_{1-4}alkanyl, phenyl, and C_{3-6}cycloalkanyl; provided

that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, hydroxy, and C_{1-6}alkanylthio; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-4}alkanyl and hydroxy.

10. The compound according to claim 1 wherein R_2 is selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, and hydroxy; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-3}alkanyl and hydroxy.

11. The compound according to claim 1 wherein R_3 is selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, thioformyl, phenylimino(C_{1-8})alkanyl,

phenyl(C_{1-8})alkanyl, and heteroaryl(C_{1-8})alkanyl wherein heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, indolyl, indolinyl, isoquinolinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl; wherein phenyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyloxy and hydroxy; or optionally, when phenyl and heteroaryl are optionally substituted with two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the moiety is selected from $-O(CH_2)_{1-3}O-$.

12. The compound according to claim 1 wherein R_3 is selected from the group consisting of hydrogen, methyl, allyl, 2-methyl-allyl, propynyl, hydroxyethyl, methylthioethyl, methoxyethyl, thioformyl, phenyliminomethyl, phenethyl, and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl; wherein the phenyl in any phenyl-containing substituent is optionally substituted with one hydroxyl group.

13. The compound according to claim 1 wherein R_3 is hydrogen, methyl, allyl, or heteroarylmethyl wherein heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, and thienyl.

14. The compound according to claim 1 wherein R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{1-6}alkanyloxy, aminocarbonyl, aminothiocarbonyl, hydroxyamidino, formylamino, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, halogen, hydroxy, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl,

indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, and thienyl.

15. The compound according to claim 1 wherein R_4 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, hydroxy, and aminocarbonyl.

16. The compound according to claim 1 wherein R_4 is one to two substituents independently selected from the group consisting of hydrogen, methyl, methoxy, bromo, fluoro, 5- or 6-phenyl, 5- or 6-pyridinyl, 5- or 6-furanyl, and hydroxy.

17. The compound according to claim 1 wherein R_5 is one to two substituents independently selected from the group consisting of hydrogen and halogen.

18. The compound according to claim 1 wherein R_5 is hydrogen.

19. The compound according to claim 1 wherein A is absent or $-(CH_2)_2-$.

20. The compound according to claim 1 wherein A is $-(CH_2)_2-$.

21. The compound according to claim 1 wherein X is O or S.

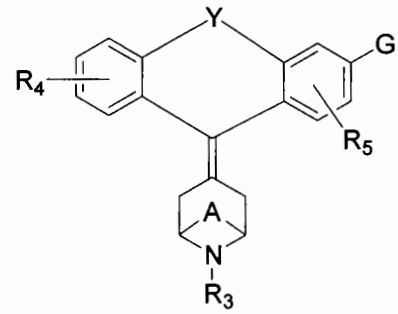
22. The compound according to claim 1 wherein n is 0.

23. The compound according to claim 1 wherein Z is O, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl).

24. The compound according to claim 1 wherein Z is O, NH, or N(OH).

25. The compound according to claim 1 wherein Z is O or NH.

26. A compound of Formula (I):



Formula (I)

wherein:

G is –C(Z)NR_1R_2, phenyl, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, aminocarbonyl, aminothiocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

R_1 is hydrogen or C_{1-4}alkanyl;

R_2 is selected from the group consisting of hydrogen; C_{1-4}alkanyl; phenyl; and C_{3-6}cycloalkanyl; provided that when Z is O or S, R_2 is other than hydrogen or unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-4}alkanyloxy, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl and C_{3-6}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{1-8}alkanyloxy, trifluoromethyl, phenyl, fluoro, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with C_{1-4}alkanyloxy or hydroxy), C_{1-4}alkanyl, or hydroxy;

R_3 is selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, thioformyl, phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, and heteroaryl(C_{1-8})alkanyl wherein heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, indolyl, indolinyl, isoquinolinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl; wherein phenyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyloxy and hydroxy; or optionally, when phenyl and heteroaryl are optionally substituted with two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the moiety is selected from $-O(CH_2)_{1-3}O-$;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{1-6}alkanyloxy, aminocarbonyl, aminothiocarbonyl, hydroxyamidino, formylamino, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, halogen, hydroxy, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, and thienyl;

R_5 is one to two substituents independently selected from the group consisting of hydrogen and halogen;

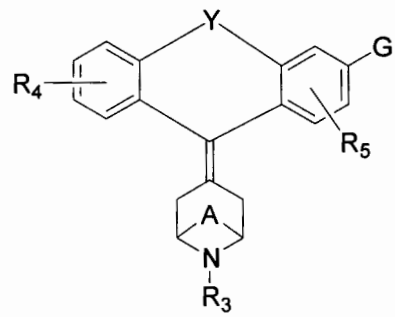
A is absent or $-(CH_2)_2-$;

Y is O, S, CH_2O or OCH_2;

Z is O, NH, $N(C_{1-6}alkanyl)$, N(OH), $N(OC_{1-6}alkanyl)$, or N(phenyl); and

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

27. A compound of Formula (I):



Formula (I)

wherein:

G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group consisting of imidazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group

consisting of C_{1-4}alkanyl, C_{1-4}alkanyloxy, hydroxy(C_{1-4})alkanyl, carboxy(C_{1-4})alkanyl, C_{1-4}alkanylcarbonylamino, hydroxy, cyano, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, aminocarbonyl, aminothiocarbonyl, C_{1-8}alkanylaminocarbonyl, and di(C_{1-8}alkanyl)aminocarbonyl;

R_1 is selected from the group consisting of hydrogen, methyl, ethyl, and propyl;

R_2 is selected from the group consisting of C_{1-4}alkanyl, phenyl, and C_{3-6}cycloalkanyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, hydroxy, and C_{1-6}alkanylthio; or R_1 and R_2 taken together with the nitrogen to which they are attached form pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from the group consisting of C_{1-3}alkanyl and hydroxy;

R_3 is selected from the group consisting of hydrogen, methyl, allyl, 2-methyl-allyl, propynyl, hydroxyethyl, methylthioethyl, methoxyethyl, thioformyl, phenyliminomethyl, phenethyl, and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl; wherein the phenyl in any phenyl-containing substituent is optionally substituted with one hydroxyl group;

R_4 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl,

furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, hydroxy, and aminocarbonyl;

R_5 is hydrogen;

A is $-(CH_2)_2-$;

Y is O or S;

Z is O, NH, or N(OH); and

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

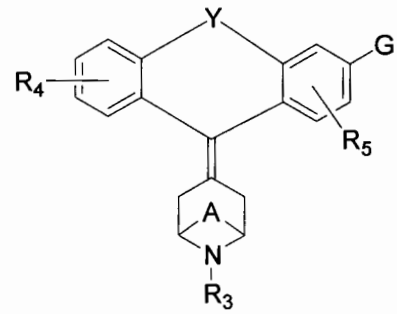
28. The compound according to claim 27 wherein G is $-C(Z)NR_1R_2$, phenyl, or a heterocycle selected from the group consisting of imidazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, thienyl, isothiazolyl, isoxazolyl, isoxadiazolyl, quinolinyl, and pyridinyl; wherein phenyl and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4}alkanyl, C_{1-4}alkanyloxy, hydroxy(C_{1-4})alkanyl, C_{1-4}alkanylcarbonylamino, hydroxy, cyano, oxo, thioxo, and aminocarbonyl.

29. The compound according to claim 27 wherein G is $-C(Z)NR_1R_2$, 2-methylcarbonylaminophenyl, 2-aminocarbonyl-phenyl, 1*H*-tetrazol-5-yl, 2-methyl-tetrazol-5-yl, 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl, 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl, 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl, [1,2,3,5]oxathiadiazol-2-oxo-4-yl, or pyridin-3-yl.

30. The compound according to claim 27 wherein R_2 is selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently

selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, and hydroxy; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from C_{1-3}alkanyl or hydroxy; and R_3 is a substituent selected from the group consisting of benzo[1,3]dioxol-5-ylmethyl, carbamimidoyl, 1-*H*-imidazol-4-ylmethyl, phenyliminomethyl, 1-prop-2-ynyl, thioformyl, 2-hydroxyphenyl-methyl, hydroxy-ethyl, methoxy-ethyl, 2-methyl-allyl, 2-methyl-but-2-enyl, allyl, furan-3-ylmethyl, H, Me, methylthioethyl, phenethyl, pyridin-2-yl methyl, and thiophen-2-yl methyl.

31. A compound of Formula (I):



Formula (I)

wherein:

G is selected from –C(Z)NR_1R_2, 2-methylcarbonylaminophenyl, 2-aminocarbonyl-phenyl, 1*H*-tetrazol-5-yl, 2-methyl-tetrazol-5-yl, 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl, 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl, 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl, [1,2,3,5]oxathiadiazol-2-oxo-4-yl, or pyridin-3-yl;

R_1 is hydrogen, methyl, or ethyl;

R_2 is selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and,

wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, fluoro, and phenoxy; wherein the phenyl and phenoxy substituents of C_{1-4}alkanyl are optionally further substituted with, and the phenyl of R_2 is optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, and hydroxy; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from C_{1-3}alkanyl or hydroxy;

R_3 is selected from the group consisting of hydrogen, methyl, allyl, 2-methyl-allyl, propynyl, hydroxyethyl, methylthioethyl, methoxyethyl, thioformyl, phenyliminomethyl, phenethyl, and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl; wherein the phenyl in any phenyl-containing substituent is optionally substituted with one hydroxyl group;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, hydroxy, and aminocarbonyl;

R_5 is hydrogen;

A is $-(CH_2)_2-$;

Y is O or S;

Z is O or NH; and

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

32. The compound according to claim 31 wherein R_2 is a substituent

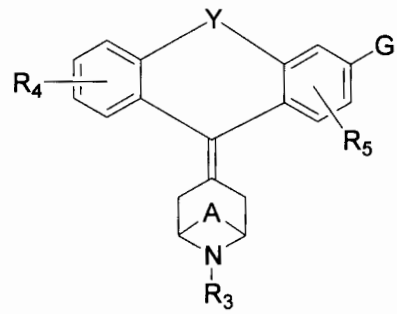
selected from the group consisting of C_{1-4}alkanyl and phenyl; provided that when Z is O or S, R_2 is other than unsubstituted C_{1-4}alkanyl; and, wherein C_{1-4}alkanyl is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, C_{1-4}alkanyloxy, hydroxy, and 2,6-dimethyl-phenoxy; one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkanyloxy, fluoro, and hydroxy; or R_1 and R_2 taken together with the nitrogen to which they are attached form a pyrrolidinyl or piperidinyl ring wherein said pyrrolidinyl or piperidinyl is optionally substituted with a substituent selected from C_{1-3}alkanyl or hydroxy.

33. The compound according to claim 31 wherein R_3 is a substituent selected from the group consisting of benzo[1,3]dioxol-5-ylmethyl, carbamimidoyl, 1-*H*-imidazol-4-ylmethyl, phenyliminomethyl, 1-prop-2-ynyl, thioformyl, 2-hydroxyphenyl-methyl, hydroxy-ethyl, methoxy-ethyl, 2-methyl-allyl, 2-methyl-but-2-enyl, allyl, furan-3-ylmethyl, H, Me, methylthioethyl, phenethyl, pyridin-2-yl methyl, and thiophen-2-ylmethyl; and R_4 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-4}alkanyl, C_{1-4}alkanyloxy, halogen, phenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinolinyl, tetrazolyl, thiazolyl, thienyl, and hydroxy.

34. The compound according to claim 31 wherein R_3 is a substituent selected from the group consisting of benzo[1,3]dioxol-5-ylmethyl, carbamimidoyl, 1-*H*-imidazol-4-yl methyl, phenyliminomethyl, 1-prop-2-ynyl, thioformyl, 2-hydroxyphenyl-methyl, hydroxyethyl, methoxyethyl, allyl, furan-3-yl methyl, H, Me, methylthioethyl, and phenethyl; R_4 is one to two substituents independently selected from the group consisting of hydrogen, methyl, methoxy, bromo, fluoro, 5- or 6-phenyl, 5- or 6-pyridinyl, 5- or 6-furanyl, and hydroxy.

35. The compound according to claim 31 wherein R_3 is a substituent selected from the group consisting of H, benzo[1,3]dioxol-5-ylmethyl, 1-*H*-imidazol-4-yl methyl, furan-3-ylmethyl, pyridin-2-ylmethyl, and phenyliminomethyl; and R_4 is a substituent independently selected from the group consisting of hydrogen, methyl, methoxy, bromo, fluoro, 5- or 6-phenyl, 5- or 6-pyridinyl, 5- or 6-furanyl, and hydroxy.

36. A compound of Formula (I):



Formula (I)

selected from the group consisting of:

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is [1,2,3,5]oxathiadiazol-2-oxo-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(3-fluorophenyl)-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl]aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-phenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminocarbonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-phenylethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-cyclohexyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-hydroxymethyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-hydroxyamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 5-ethyl-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*R*)-hydroxymethyl-2-phenyl-eth-1-yl)-aminocarbonyl ;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N, N*-diisobutylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1*S*-methoxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methoxypyridin-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4,5-dihydro-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(4-phenyl)-cyclohexyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methyl-4H-[1,2,4]triazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 5-methyl-[1,2,4]oxadiazol-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-1-methoxycarbonyl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-hydroxy-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is isopropylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylmethylaminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1,4,5,6-tetrahydropyrimidin-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-aminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *C*-piperidin-1-yl-methyleneamine; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methoxyphenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is cyclopentylaminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylphenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylaminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*- bis (2,2,2-trifluoro-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is isobutylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *C*-morpholin-4-yl-methyleneamine; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-fluorophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-benzyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-methanesulfonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-fluorophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is thiophen-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methoxyphenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylmethylaminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylaminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is cyclopentylaminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[(4-trifluoromethyl)-cyclohexyl]-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methanesulfonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-2,2,2,-trifluoroethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-[(3-methoxy)phenyl]piperidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-4-fluorophenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*R*)-hydroxymethyl-3-methyl-but-1-yl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(dimethylaminocarbonylmethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*R*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*S*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is phenylthio; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-hydroxy;R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-1,1-dimethyl-ethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is fur-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is thien-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-4-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-pyrazol-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is methyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is 1*H*-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is methyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is 1H-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-aminocarbonyl; R_3 is *t*-butoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*R*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

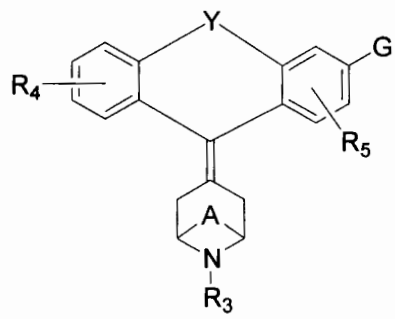
a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O; and

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O.

37. A compound of Formula (I):



Formula (I)

selected from the group consisting of:

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is [1,2,3,5]oxathiadiazol-2-oxo-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(3-fluorophenyl)-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl]aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-phenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminocarbonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-phenylethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-cyclohexyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-hydroxymethyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-hydroxyamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 5-ethyl-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*R*)-hydroxymethyl-2-phenyl-eth-1-yl)-aminocarbonyl ;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N, N*-diisobutylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1*S*-methoxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methoxypyridin-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4,5-dihydro-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(4-phenyl)-cyclohexyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methyl-4H-[1,2,4]triazol-5-yl;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methanesulfonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-2,2,2,-trifluoroethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-[(3-methoxy)phenyl]piperidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-4-fluorophenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(dimethylaminocarbonylmethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*R*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*S*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-1,1-dimethyl-ethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is fur-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is thien-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-4-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is 5-methoxy;R_5 is H; and Y is O;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-pyrazol-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is methyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is 1*H*-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is pyridin-2-ylmethyl;R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is 1H-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is *N*-(2-hydroxy-ethyl)-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

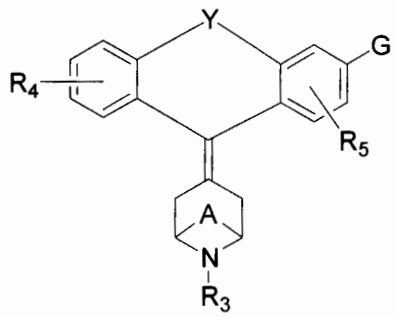
a compound of Formula (I) wherein G is (3(*R*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O; and

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O.

38. A compound of Formula (I):



Formula (I)

selected from the group consisting of:

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is [1,2,3,5]oxathiadiazol-2-oxo-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(3-fluorophenyl)-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl]aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-phenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminocarbonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-phenylethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-cyclohexyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-hydroxymethyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-hydroxyamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 5-ethyl-1*H*-imidazol-2-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*R*)-hydroxymethyl-2-phenyl-eth-1-yl)-aminocarbonyl ;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-2,2,2,-trifluoroethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-[(3-methoxy)phenyl]piperidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-4-fluorophenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(dimethylaminocarbonylmethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is (3(*S*)-hydroxy)pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is fur-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is 1*H*-imidazol-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is pyridin-2-ylmethyl;R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is fur-3-ylmethyl; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

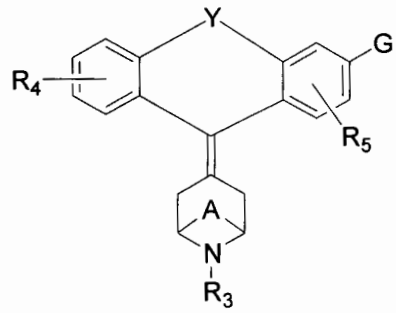
a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O; and

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O.

39. A compound of Formula (I):



Formula (I)

selected from the group consisting of:

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylaminophenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyrrolidin-1-ylcarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-methoxy-ethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is [1,2,3,5]oxathiadiazol-2-oxo-4-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(3-fluorophenyl)-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-[2-(2,6-dimethylphenoxy)-1-methyl-ethyl]aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-phenyl-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(1(*S*)-hydroxymethyl-2-phenyl-eth-1-yl)aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methyl-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-phenylethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-aminocarbonyl-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-phenylethyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 3-methylcarbonylamino-phenyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(2-dimethylamino-eth-1-yl)-*N*-methyl-aminocarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is *N*-(dimethylaminocarbonylmethyl)-*N*-methyl-aminocarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is pyridin-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]thiadiazol-5-oxo-3-yl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 1*H*-tetrazol-5-yl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is quinolin-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 2-methylcarbonylamino-phenyl; R_3 is pyridin-2-ylmethyl; R_4 is H; R_5 is H; and Y is S;

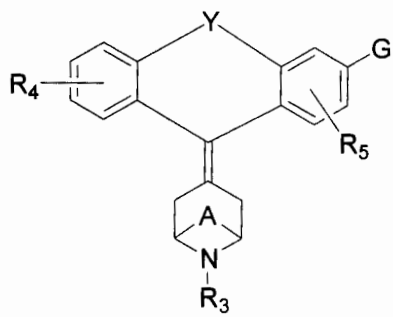
a compound of Formula (I) wherein G is *N,N*-diethylamidino; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-thioxo-3-yl; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O; and

a compound of Formula (I) wherein G is 4*H*-[1,2,4]-oxadiazol-5-oxo-3-yl; R_3 is H; R_4 is 5-hydroxy; R_5 is H; and Y is O.

40. A compound of Formula (Ib):



Formula (Ib)

selected from the group consisting of:

a compound of Formula (Ib) wherein G is carboxy; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is ethoxycarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (Ib) wherein G is cyano; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is methoxycarbonyl; R_3 is H; R_4 is 6-methoxycarbonyl; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is bromo; R_3 is H; R_4 is 5-methoxy; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is bromo; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (Ib) wherein G is cyano; R_3 is H; R_4 is H; R_5 is H; and Y is S;

a compound of Formula (Ib) wherein G is cyano; R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is cyano;R_3 is H; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is cyano; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is cyano; R_3 is trifluoromethylcarbonyl; R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is carboxy; R_3 is t-Butoxycarbonyl;R_4 is H; R_5 is H; and Y is O;

a compound of Formula (Ib) wherein G is carboxy;R_3 is H; R_4 is H; R_5 is H; and Y is O; and

a compound of Formula (Ib) wherein G is carboxy;R_3 is H; R_4 is H; R_5 is H; and Y is O.

41. A composition comprising the dextrorotatory enantiomer of a compound of of formula (I) wherein said composition is substantially free from the levorotatory isomer of said compound.

42. A composition comprising the levororotatory enantiomer of a compound of formula (I) wherein said composition is substantially free from the dextrorotatory isomer of said compound.

43. A pharmaceutical composition comprising a compound, salt or solvate according to any of claims 1 admixed with a pharmaceutically acceptable carrier, excipient or diluent.

44. A veterinary composition comprising a compound, salt or solvate according to claim 1 admixed with a veterinarily acceptable carrier, excipient or diluent.

45. A method of treating or preventing a disease or condition in a mammal which disease or condition is affected by the modulation of delta opioid receptors, which method comprises administering to a mammal in need of such treatment or prevention a therapeutically effective amount of a compound, salt or solvate of claim 1.

46. The method of claim 45 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

47. The method of claim 45 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

48. The method of claim 45 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.

49. A method for preventing or treating mild to severe pain comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, salt or solvate of claim 1.

50. The method of claim 49 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 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.

51. The method of claim 49 wherein the pain is caused by 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, cellulites, 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, post-herpetic neuralgia, trigeminal neuralgia, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial 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.

52. 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, salt or solvate of claim 1.

53. The method of claim 49 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

54. The method of claim 49 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

55. The method of claim 49 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.

56. A kit comprising in one or more containers an amount of the composition of claim 1 effective to treat or prevent mild to severe pain.

57. A pharmaceutical composition comprising a compound, salt or solvate according to claim 26 admixed with a pharmaceutically acceptable carrier, excipient or diluent.

58. A veterinary composition comprising a compound, salt or solvate according to claim 26 admixed with a veterinarily acceptable carrier,

excipient or diluent.

59. A method for preventing or treating mild to severe pain, said method comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, salt or solvate of claim 26.

60. The method of claim 59 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 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.

61. The method of claim 59 wherein the pain is caused by 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, cellulites, 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, post-herpetic neuralgia, trigeminal neuralgia, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial

neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial 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.

62. 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, cancer/pain, 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, salt or solvate of claim 26.

63. The method of claim 59 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

64. The method of claim 59 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

65. The method of claim 59 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.

66. A kit comprising in one or more containers an amount of the composition of claim 26 effective to treat or prevent mild to severe pain.

67. A pharmaceutical composition comprising a compound, salt or solvate according to claim 31 admixed with a pharmaceutically acceptable carrier, excipient or diluent.

68. A veterinary composition comprising a compound, salt or solvate according to claim 31 admixed with a veterinarily acceptable carrier, excipient or diluent.

69. A method for preventing or treating mild to severe pain, said method comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, salt or solvate of claim 31.

70. The method of claim 69 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 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.

71. The method of claim 69 wherein the pain is caused by 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, cellulites, 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, post-herpetic neuralgia, trigeminal neuralgia, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, optic neuritis, postfebrile neuritis, migrating neuritis,

segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial 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.

72. 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, salt or solvate of claim 31.

73. The method of claim 69 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

74. The method of claim 69 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

75. The method of claim 69 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.

76. A kit comprising in one or more containers an amount of the composition of claim 31 effective to treat or prevent mild to severe pain.

77. A pharmaceutical composition comprising a compound, salt or solvate according to claim 36 admixed with a pharmaceutically acceptable carrier, excipient or diluent.

78. A veterinary composition comprising a compound, salt or solvate according to claim 36 admixed with a veterinarily acceptable carrier, excipient or diluent.

79. A method for preventing or treating mild to severe pain, said method comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, salt or solvate of claim 36.

80. The method of claim 79 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 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.

81. The method of claim 79 wherein the pain is caused by 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, cellulites, 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, post-herpetic neuralgia, trigeminal neuralgia, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia,

trigeminal neuralgia, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial 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.

82. 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, salt or solvate of claim 36.

83. The method of claim 79 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

84. The method of claim 79 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

85. The method of claim 79 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.

86. A kit comprising in one or more containers an amount of the composition of claim 36 effective to treat or prevent mild to severe pain.

87. A pharmaceutical composition comprising a compound, salt or solvate according to claim 37 admixed with a pharmaceutically acceptable carrier, excipient or diluent.

88. A veterinary composition comprising a compound, salt or solvate according to claim 37 admixed with a veterinarily acceptable carrier, excipient or diluent.

89. A method for preventing or treating mild to severe pain, said method comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, salt or solvate of claim 37.

90. The method of claim 89 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 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.

91. The method of claim 89 wherein the pain is caused by 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, cellulites, 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, post-herpetic neuralgia, trigeminal neuralgia, cluster headache, migraine headache, peripheral neuropathy, bilateral

peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial 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.

92. 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, salt or solvate of claim 37.

93. The method of claim 89 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

94. The method of claim 89 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

95. The method of claim 89 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.

96. A kit comprising in one or more containers an amount of the composition of claim 37 effective to treat or prevent mild to severe pain.

97. A pharmaceutical composition comprising a compound, salt or solvate according to claim 38 admixed with a pharmaceutically acceptable carrier, excipient or diluent.

98. A veterinary composition comprising a compound, salt or solvate according to claim 38 admixed with a veterinarily acceptable carrier, excipient or diluent.

99. A method for preventing or treating mild to severe pain, said method comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, salt or solvate of claim 38.

100. The method of claim 99 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 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.

101. The method of claim 99 wherein the pain is caused by 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, cellulites, 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, post-herpetic neuralgia, trigeminal neuralgia, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial 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.

102. 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, salt or solvate of claim 38.

103. The method of claim 99 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

104. The method of claim 99 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

105. The method of claim 99 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.

106. A kit comprising in one or more containers an amount of the composition of claim 38 effective to treat or prevent mild to severe pain.

107. A pharmaceutical composition comprising a compound, salt or solvate according to claim 39 admixed with a pharmaceutically acceptable carrier, excipient or diluent.

108. A veterinary composition comprising a compound, salt or solvate according to claim 39 admixed with a veterinarily acceptable carrier, excipient or diluent.

109. A method for preventing or treating mild to severe pain, said method comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a compound, salt or solvate of claim 39.

110. The method of claim 109 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 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.

111. The method of claim 109 wherein the pain is caused by 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, cellulites, 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, post-herpetic neuralgia, trigeminal neuralgia, cluster headache, migraine headache, peripheral neuropathy, bilateral peripheral neuropathy, diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, optic neuritis, postfebrile neuritis, migrating neuritis, segmental neuritis, Gombault's neuritis, neuronitis, cervicobrachial neuralgia, cranial neuralgia, geniculate neuralgia, glossopharyngial 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.

112. 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, salt or solvate of claim 39.

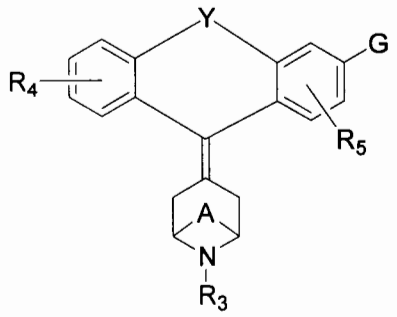
113. The method of claim 109 wherein said therapeutically effective amount comprises a dose range of from about 0.1 mg to about 1,000 mg.

114. The method of claim 109 wherein said therapeutically effective amount comprises a dose range of from about 50 mg to about 1000 mg.

115. The method of claim 109 wherein said therapeutically effective amount comprises a dose range of from about 100 mg to about 1000 mg.

116. A kit comprising in one or more containers an amount of the composition of claim 39 effective to treat or prevent mild to severe pain.

117. A compound of Formula (Ib):



Formula (Ib)

wherein:

G is bromo, chloro, cyano, trifluoromethanesulfonyloxy, C_{1-8}alkanyloxycarbonyl, carboxy, $-C(Z)NR_1R_2$, C_{6-10}aryl, C_{6-10}arylthio, or a heterocycle selected from the group consisting of imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, oxathiadiazolyl, imidazolinyl, tetrahydropyrimidinyl, thienyl, pyrazolyl, pyrimidinyl, triazinyl, furyl, indazolyl, indolyl, indolinyl, isothiazolyl, isoxazolyl, oxazolyl, isoxadiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, and pyridinyl; wherein the C_{6-10}aryl group in the C_{6-10}aryl-containing substituents of G and the heterocycles of G are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, hydroxy(C_{1-8})alkanyl, carboxy(C_{1-8})alkanyl, C_{1-8}alkanylcarbonylamino, halogen, hydroxy, cyano, nitro, oxo, thioxo, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, C_{1-8}alkanylsulfonylamino, aminocarbonyl, aminothiocarbonyl, aminocarbonylamino, aminothiocarbonylamino,

C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, and C_{1-6}alkanyloxycarbonylamino;

R_1 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, C_{2-8}alkenyl, and C_{2-8}alkynyl;

R_2 is a substituent selected from the group consisting of hydrogen; C_{1-8}alkanyl; C_{2-8}alkenyl; C_{2-8}alkynyl; C_{6-10}aryl; and C_{3-8}cycloalkanyl; provided that when Z is O or S, R_2 is other than hydrogen or unsubstituted C_{1-8}alkanyl; and, wherein C_{1-8}alkanyl of R_2 is optionally substituted with one to three substituents independently selected from the group consisting of phenyl, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanyloxy, C_{1-6}alkanylthio, hydroxy, fluoro, chloro, cyano, aminocarbonyl, C_{1-8}alkanylaminocarbonyl, di(C_{1-8}alkanyl)aminocarbonyl, C_{1-6}alkanyloxycarbonyl, and aryloxy; wherein the phenyl and aryloxy substituents of C_{1-8}alkanyl are optionally further substituted with, and the C_{6-10}aryl and C_{3-8}cycloalkanyl substituents of R_2 are optionally substituted with, one to three substituents independently selected from the group consisting of C_{1-8}alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{1-8}alkanyloxy, trifluoromethyl, trifluoromethoxy, phenyl, halogen, cyano, hydroxy, C_{1-8}alkanylthio, C_{1-8}alkanylsulfonyl, and C_{1-8}alkanylsulfonylamino;

or R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with phenyl (wherein phenyl is optionally substituted with one to three C_{1-4}alkanyl or C_{1-4}alkanyloxy substituents) and one to two additional substituents independently selected from the group consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

or, R_1 and R_2 taken together with the nitrogen to which they are attached form a 5-7 membered cycloheteroalkyl optionally substituted with one to three substituents independently selected from the group

consisting of C_{1-8}alkanyl, hydroxy(C_{1-8})alkanyl, hydroxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, and halogen;

R_3 is a substituent selected from the group consisting of hydrogen, C_{1-8}alkanyl, halo$_{1-3}$(C_{1-8})alkanyl, C_{2-8}alkenyl, C_{2-8}alkynyl, C_{3-8}cycloalkanyl, cycloalkanyl(C_{1-8})alkanyl, C_{1-8}alkanyloxy(C_{1-8})alkanyl, C_{1-8}alkanylthio(C_{1-8})alkanyl, hydroxyC_{1-8}alkanyl, C_{1-8}alkanyloxycarbonyl, halo$_{1-3}$(C_{1-8})alkanylcarbonyl, formyl, thioformyl, carbamimidoyl, phenylimino(C_{1-8})alkanyl, phenyl(C_{1-8})alkanyl, phenyl(C_{1-8})alkenyl, phenyl(C_{1-8})alkynyl, naphthyl(C_{1-8})alkanyl and heteroaryl(C_{1-8})alkanyl wherein the heteroaryl is selected from the group consisting of benzo[1,3]dioxolyl, imidazolyl, furanyl, pyridinyl, thienyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinolinyl, isoquinolinyl, tetrazolyl, thiazolyl; wherein phenyl, naphthyl and heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl, thioureido, and fluoro(C_{1-6})alkanyloxy; alternatively, when phenyl and heteroaryl are optionally substituted with alkanyl or alkanyloxy substituents attached to adjacent carbon atoms, the two substituents can together form a fused cyclic alkanyl or cycloheteroalkanyl selected from the group consisting of -$(CH_2)_{3-5}$- , -O$(CH_2)_{2-4}$- , -$(CH_2)_{2-4}$O -, and -O$(CH_2)_{1-3}$O-;

R_4 is one to three substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{2-6}alkynyl, aryl(C_{2-6})alkynyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy,

C_{1-6}alkanyloxycarbonyl, aminocarbonyl, C_{1-6}alkanylaminocarbonyl, di(C_{1-6}alkanyl)aminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, mercapto, aminothiocarbonyl, amidino, hydroxyamidino, phenylcarbonyl, -C(=NOH)phenyl, aminomethyl, hydroxymethyl, methanesulfonylamino, C_{6-10}arylamino (wherein C_{6-10}aryl is optionally substituted with one to three substitutents independently selected from the group consisting of C_{1-6}alkanyl, C_{1-6}alkoxy, halogen, and hydroxy), dihydroimidazolyl, formylamino, thioformylamino, pyridinylamino, cyano, hydroxycarbonyl, C_{6-10}aryl, chromanyl, chromenyl, furanyl, imidazolyl, indazolyl, indolyl, indolinyl, isoindolinyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrazolyl, thiazolyl, thienyl, fluoroalkanyl and fluoroalkanyloxy; or optionally, when R_4 is two substituents attached to adjacent carbon atoms, the two substituents together form a single fused moiety; wherein the fused moiety is selected from the group consisting of -$(CH_2)_{3-5}$-, -$O(CH_2)_{2-4}$- , -$(CH_2)_{2-4}O$-, -$O(CH_2)_{1-3}O$- and -S-$C(NH_2)$=N-;

R_5 is one to two substituents independently selected from the group consisting of hydrogen, C_{1-6}alkanyl, C_{2-6}alkenyl, C_{1-6}alkanyloxy, amino, C_{1-6}alkanylamino, di(C_{1-6}alkanyl)amino, C_{1-6}alkanylcarbonyl, C_{1-6}alkanylcarbonyloxy, C_{1-6}alkanyloxycarbonyl, C_{1-6}alkanylaminocarbonyl, C_{1-6}alkanylcarbonylamino, C_{1-6}alkanylthio, C_{1-6}alkanylsulfonyl, halogen, hydroxy, cyano, fluoro(C_{1-6})alkanyl and fluoro(C_{1-6})alkanyloxy;

A is absent or –$(CH_2)_m$–, wherein m is 2 or 3;

Y is -$(CH_2)_n$X- or -X$(CH_2)_n$-;

X is O or S

n is 0 or 1;

Z is O, S, NH, N(C_{1-6}alkanyl), N(OH), N(OC_{1-6}alkanyl), or N(phenyl); and enantiomers, diastereomers, tautomers, solvates, or pharmaceutically acceptable salts thereof.

118. The compound according to claim 117 wherein G is bromo or cyano.