HYDROXY ALKYL SUBSTITUTED 1,3,8-TRIAZASPIRO[4.5]DECAN-4-ONE DERIVATIVES USEFUL FOR THE TREATMENT OF ORL-1 RECEPTOR MEDIATED DISORDERS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U. S. Provisional Application 60/409,134, filed on September 09, 2002, which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

The present invention is directed to novel hydroxy alkyl substituted 1,3,8-triazaspiro[4.5]decan-4-one derivatives useful in the treatment of disorders and conditions mediated by the ORL-1 G-protein coupled receptor. More particularly, the compounds of the present invention are useful in the treatment of disorders and conditions such as anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization.

BACKGROUND OF THE INVENTION

The ORL-1 (orphan opioid receptor) G-protein coupled receptor, also known as the nociceptin receptor, was first reported in 1994, and was discovered based on its homology with the classic delta- (OP-1), mu- (OP-3), and kappa- (OP-2) opioid receptors. The ORL-1 G-protein coupled receptor does not bind opioid ligands with high affinity. The amino acid sequence of ORL-1 is 47% identical to the opioid receptors overall, and 64% identical in the transmembrane domains. (*Nature*, **1995**, *377*, 532.)

The endogenous ligand of ORL-1, known as nociceptin, a highly basic 17 amino acid peptide, was isolated from tissue extracts in 1995. It was named both nociceptin, because it increased sensitivity to pain when injected into mouse brain, and orphanin FQ (OFQ) because of the terminal phenylalanine (F) and glutamine (Q) residues that flank the peptide on the N- and C-termini respectively. (WO97/07212)

Nociceptin binding to ORL-1 receptors causes inhibition of cAMP synthesis, inhibition of voltage-gated calcium channels, and activation of potassium conductance. In vivo, nociceptin produces a variety of pharmacological effects that at times oppose those of the opioids, including hyperalgesia and inhibition of morphine-induced analgesia. Mutant mice lacking nociceptin receptors show better performance in learning and memory tasks. These mutant mice also have normal responses to painful stimuli.

The ORL-1 receptor is widely distributed / expressed throughout the human body, including in the brain and spinal cord. In the spinal cord, the ORL-1 receptor exists in both the dorsal and ventral horns, and precursor mRNA has been found in the superficial lamina of the dorsal horn, where primary afferent fibers of nociceptors terminate. Therefore, the ORL-1 has an important role in nociception transmission in the spinal cord. This was confirmed in recent studies wherein nociceptin, when given to mice by i.c.v. injection, induced hyperalgesia and decreased locomotor activity. (*Brit. J. Pharmacol.* **2000**, *129*, 1261.)

Ito, et al., in EP 0997464 disclose 1,3,8-triazaspiro[4.5]decan-4-one compounds as ORL-1 receptor agonists, useful as analgesics or the like in mammalian subjects.

Hohlweg et al., in PCT publication WO 01/36418 disclose triazaspirodecanones with high affinity for opioid receptor subtypes useful in the treatment of migraine, non-insulin dependent diabetes mellitus, sepsis, inflammation, incontinence and / or vasomotor disturbances.

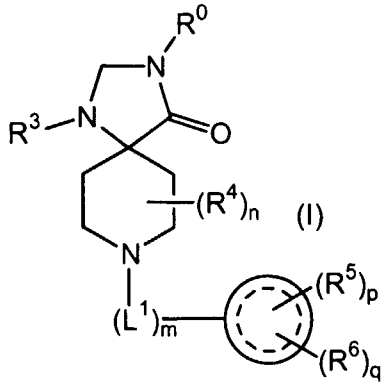
Tulshian et al. in PCT publication WO00/06545 disclose high affinity ligands for the nociceptin receptor ORL-1 and the use of said compounds as nociceptin receptor inhibitors useful in the treatment of pain, anxiety, cough, asthma, depression and alcohol abuse.

Higgins, et.al., in European Forum of Neuroscience 2000, Brighton, U.K., June 24-28, 2000, Poster 077.22 disclosed, 8-[(1R,3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one useful as cognition enhancers.

We now describe novel small molecule modulators of the ORL-1 receptor, useful for the treatment of disorders and conditions mediated by the ORL-1 receptor, such as anxiety, depression, panic, dementia, mania, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorders (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization.

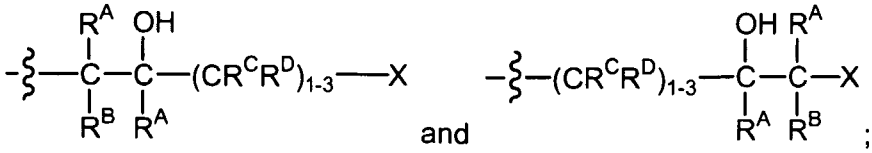
SUMMARY OF THE INVENTION

The present invention is directed to compounds of the general formula (I)



wherein

R^0 is selected from the group consisting of



and ;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

each R^C and R^D is independently selected from the group consisting of hydrogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl; wherein the aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl substituent is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano or $N(R^E)_2$;

each R^E is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-NR^1-C(O)O-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one or more substituents independently selected from carboxy, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxycarbonyl or $-CONR^1R^2$;

each R^1 and R^2 is independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-8}alkoxycarbonyl, cycloalkyl, cycloalkyl-C_{1-4}alkyl, partially unsaturated carbocyclyl, partially unsaturated carbocyclyl-C_{1-4}alkyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkoxy, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, $-C(O)-C_{1-6}$alkyl, -C(O)-aryl, -C(O)-arC_{1-4}alkyl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -C(O)O-cycloalkyl and –C(O)O-aryl, -C(O)O-arC_{1-4}akyl, -C(O)O-(partially unsaturated carbocyclyl), C(O)-heteroaryl, -C(O)O-heterocycloalkyl; wherein the C_{1-8}alkyl, cycloalkyl, partially unsaturated carbocyclyl, aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl group, whether alone or part of a substituent group, is optionally substituted

with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, C(O)-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl, $N(R^E)$-$C(O)C(CH_3)_3$, -C_{1-4}alkyl-$N(R^E)$-C(O)O-C_{1-4}alkyl and -$N(R^E)$-C(O)O-C_{1-4}alkyl, aryl, aryloxy, cycloalkyl, heteroaryl, aryl substituted heteroarylaminosulfonyl or C_{1-6}alkylthio;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, hydroxy substituted C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4}alkyl, heteroaryl, heterocycloalkyl, di(C_{1-6})alkylamino-carbonyl, C_{1-4}alkoxycarbonyl-$N(R^E)$- or arylamino-C_{1-4}alkyl; wherein the aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl substituent is optionally further substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, phenyl or substituted phenyl; wherein the substituents on the phenyl are one or more independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

R^3 is selected from the group consisting of aryl, arC_{1-6}alkyl and heteroaryl; wherein the aryl, arC_{1-6}alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4}alkyl and hydroxy substituted C_{1-4}alkyl;

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6}alkyl and C_{3-6}alkenyl; wherein the double bond of the C_{3-6}alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6}alkyl or C_{3-6}alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6}alkyl, fluorinated C_{1-6}alkyl or C_{1-6}alkoxy;

 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6}alkyl, hydroxy substituted C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, NR^1R^2, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, $-SO-NR^1R^2$, $-SO_2-NR^1R^2$ and $-C(O)-NR^1R^2$,

q is an integer from 0 to 1;

R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

L^2 is selected from the group consisting of $-C_{1-6}$alkyl-, $-C_{2-4}$alkenyl-, $-C_{2-6}$alkynyl-, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)-$, $-C_{1-6}$alkyl-O-, $-C_{1-6}$alkyl-S-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, $-O-C_{2-6}$alkyl-O-, $-S-C_{2-6}$alkyl-S-, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$, $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, -C(O)-O- and -O-C(O)-;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.

Illustrative of the invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and any of the compounds described above. An illustration of the invention is a pharmaceutical composition made by mixing any of the compounds described above and a pharmaceutically acceptable carrier. Illustrating the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds described above and a pharmaceutically acceptable carrier.

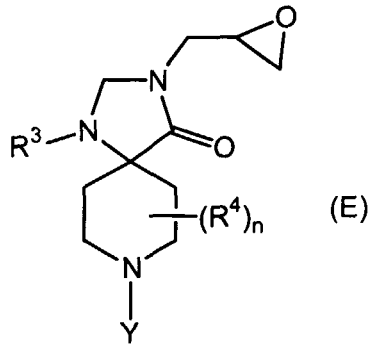
Exemplifying the invention are methods of treating disorders and conditions mediated by the ORL-1 receptor in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

An example of the invention is a method of treating a condition selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of any of the compounds or pharmaceutical compositions described above.

Another example of the invention is the use of any of the compounds described herein in the preparation of a medicament for treating: (a) anxiety, (b) depression, (c) panic, (d) mania, (e) dementia, (f) bipolar disorder, (g) substance abuse (h) neuropathic pain, (i) acute pain, (j) chronic pain, (k) migraine, (l) asthma, (m) cough, (n) psychosis, (o) schizophrenia, (p) epilepsy, (q) hypertension, (r) obesity, (s) eating disorders, (t) cravings, (u) diabetes), (v) cardiac arrhythmia, (w) irritable bowel syndrome, (x) Crohn's disease, (uy) urinary incontinence, (z) adrenal disorders, (aa) attention deficit disorder

(ADD), (bb) attention deficit hyperactivity disorder (ADHD), (cc) Alzheimer's disease, for (dd)improved cognition, (ee) improved memory and (ff) mood stabilization, in a subject in need thereof.

The present invention is further directed to a compound of formula (E)



(E)

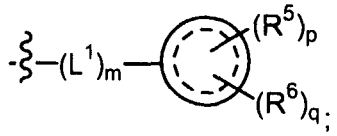
wherein

R^3 is selected from the group consisting of aryl, arC_{1-6}alkyl and heteroaryl; wherein the aryl, arC_{1-6}alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

wherein each R^E is independently selected from hydrogen or C_{1-4}alkyl;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4}alkyl and hydroxy substituted C_{1-4}alkyl;

Y is selected from the group consisting of hydrogen, C_{1-4}alkyl, t-butoxycarbonyl and ;

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6}alkyl and C_{3-6}alkenyl; wherein the double bond of the C_{3-6}alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6}alkyl or

C_{3-6}alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6}alkyl, fluorinated C_{1-6}alkyl or C_{1-6}alkoxy;

 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6}alkyl, hydroxy substituted C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, NR^1R^2, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO-NR^1R^2, -SO_2-NR^1R^2 and -C(O)-NR^1R^2;

q is an integer from 0 to 1;

R^6 is selected from the group consisting of -$(L^2)_{0-1}$-R^7;

L^2 is selected from the group consisting of -C_{1-6}alkyl-, -C_{2-4}alkenyl-, -C_{2-6}alkynyl-, -O-, -S-, -NH-, -N(C_{1-4}alkyl)-, -C_{1-6}alkyl-O-, -C_{1-6}alkyl-S-, -O-C_{1-6}alkyl-, -S-C_{1-6}alkyl-, -O-C_{2-6}alkyl-O-, -S-C_{2-6}alkyl-S-, -SO_2-, -SO_2NH-, -SO_2N(C_{1-4}alkyl)-, -NH-SO_2-, -N(C_{1-4}alkyl)-SO_2-, -C(O)-O- and -O-C(O)-;

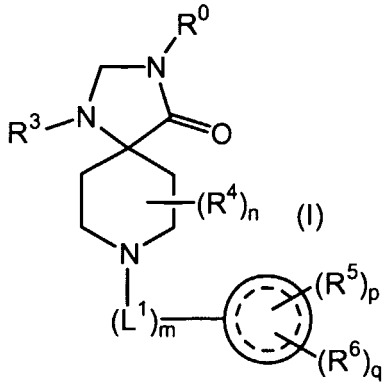
R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO_2-$N(R^E)_2$ and -C(O)-$N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides hydroxy alkyl substituted 1,3,8-triazaspiro[4.5]decan-4-one derivatives useful for the treatment of disorders

and conditions mediated by the ORL-1 receptor. More particularly, the compounds of the present invention are of the general formula (I)

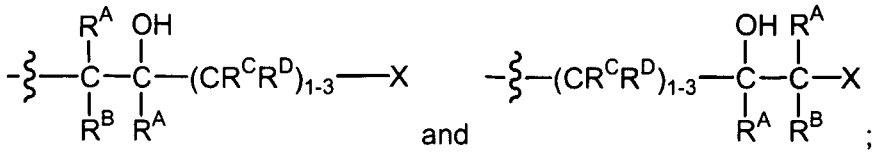


(I)

wherein R^0, R^3, n, R^4, m, L^1, , p, R^5, q and R^6 are as herein defined, or a pharmaceutically acceptable salt thereof. The compounds of formula (I) are useful in the treatment of disorders mediated by the ORL-1 receptor. The compound of formula (I) are further useful for the treatment of disorders associated with the adrenal gland.

More particularly, the compound of formula (I) are useful in the treatment of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, for improved cognition or memory and for mood stabilization. Preferably, the compounds of formula (I) are useful in the treatment of anxiety, depression, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, cough, hypertension, cardiac arrhythmia, irritable bowel syndrome and Crohn's disease.

In an embodiment of the present invention are compounds of formula (I) wherein R^0 is selected from the group consisting of



each R^A and R^B is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

each R^C and R^D is independently selected from the group consisting of hydrogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl; wherein the aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl substituent is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano or $N(R^E)_2$;

each R^E is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-NR^1-C(O)O-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one or more substituents independently selected from carboxy, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxycarbonyl or $-CONR^1R^2$;

each R^1 and R^2 is independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkoxy, cycloalkyl, cycloalkyl-C_{1-4}alkyl, partially unsaturated carbocyclyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkoxy, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, $-C(O)-C_{1-6}$alkyl, $-C(O)-$aryl, $-C(O)-$arC_{1-4}alkyl, $-C(O)-$heteroaryl and $-C(O)-$heterocycloalkyl; wherein the C_{1-8}alkyl, cycloalkyl, partially unsaturated carbocyclyl, aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $C(O)-C_{1-4}$alkyl, C_{1-4}alkoxycarbonyl, $N(R^E)_2$,

$N(R^E)_2$-C_{1-4}alkyl, $N(R^E)$-C(O)$C(CH_3)_3$, aryl, aryloxy, cycloalkyl, heteroaryl, aryl substituted heteroarylaminosulfonyl or C_{1-6}alkylthio;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4}alkyl, heteroaryl, heterocycloalkyl, di(C_{1-6})alkylamino-carbonyl, t-butoxycarbonyl or arylamino-C_{1-4}alkyl; wherein the aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl substituent is optionally further substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$ or substituted phenyl; wherein the substituents on the phenyl are one or more independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

R^3 is selected from the group consisting of aryl, arC_{1-6}alkyl and heteroaryl; wherein the aryl, arC_{1-6}alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4}alkyl and hydroxy substituted C_{1-4}alkyl;

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6}alkyl and C_{3-6}alkenyl; wherein the double bond of the C_{3-6}alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6}alkyl or C_{3-6}alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6}alkyl, fluorinated C_{1-6}alkyl or C_{1-6}alkoxy;

 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, NR^1R^2, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, $-SO-NR^1R^2$, $-SO_2-NR^1R^2$ and $-C(O)-NR^1R^2$;

q is an integer from 0 to 1;

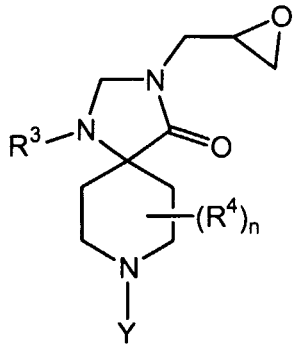
R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

L^2 is selected from the group consisting of $-C_{1-6}$alkyl-, $-C_{2-4}$alkenyl-, $-C_{2-6}$alkynyl-, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)-$, $-C_{1-6}$alkyl-O-, $-C_{1-6}$alkyl-S-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, $-O-C_{2-6}$alkyl-O-, $-S-C_{2-6}$alkyl-S-, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$, $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, -C(O)-O- and -O-C(O)-;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$;

and pharmaceutically acceptable salts thereof.

In an embodiment of the present invention are compounds of the formula (E)



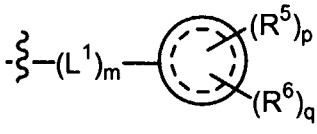
(E)

wherein R^3, n, R^4, and Y are as herein defined, or a pharmaceutically acceptable salt thereof. The compounds of formula (E) are useful as intermediates in the preparation of compounds of formula (I).

In an embodiment of the present invention are compounds of formula (E) wherein R^3 is selected from the group consisting of aryl, arC_{1-6}alkyl and heteroaryl; wherein the aryl, arC_{1-6}alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$; wherein each R^E is independently selected from hydrogen or C_{1-4}alkyl;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4}alkyl and hydroxy substituted C_{1-4}alkyl;

Y is selected from the group consisting of hydrogen, C_{1-4}alkyl, t-butoxycarbonyl and ;

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6}alkyl and C_{3-6}alkenyl; wherein the double bond of the C_{3-6}alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6}alkyl or C_{3-6}alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6}alkyl, fluorinated C_{1-6}alkyl or C_{1-6}alkoxy;

 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, NR^1R^2, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO-NR^1R^2, -SO_2-NR^1R^2 and -C(O)-NR^1R^2;

q is an integer from 0 to 1;

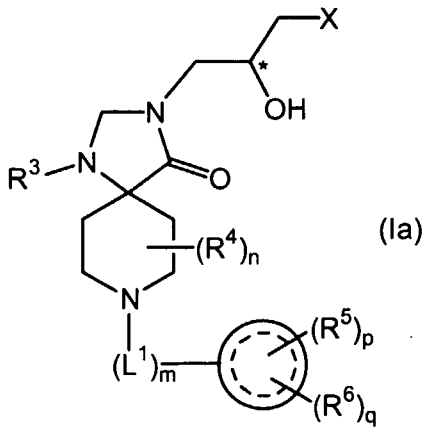
R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

L^2 is selected from the group consisting of $-C_{1-6}$alkyl-, $-C_{2-4}$alkenyl-, $-C_{2-6}$alkynyl-, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)-$, $-C_{1-6}$alkyl-O-, $-C_{1-6}$alkyl-S-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, $-O-C_{2-6}$alkyl-O-, $-S-C_{2-6}$alkyl-S-, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$, $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, -C(O)-O- and -O-C(O)-;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$;

and pharmaceutically acceptable salts thereof.

In an embodiment of the present invention are compounds of the formula (Ia)



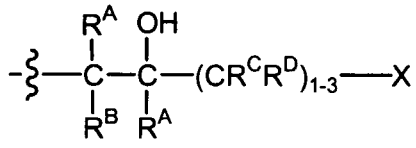
(Ia)

wherein X, R^3, n, R^4, m, L^1, , p, R^5, q and R^6 are as herein defined, or a pharmaceutically acceptable salt thereof. The compounds of formula (I) are useful in the treatment of disorders mediated by the ORL-1 receptor.

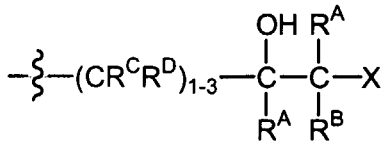
In an embodiment of the present invention is a compound of formula (I) wherein the binding of the compound to the ORL-1 receptor is 10 fold greater than the binding of the compound to the μ opioid (OP-3) receptor. In another embodiment of the present invention is a compound of formula (I) wherein the binding of the compound to the ORL-1 receptor is 100 fold greater, preferably 500 fold greater, more preferably 1000 fold greater, than the binding of the compound to the μ opioid (OP-3) receptor.

In an embodiment of the present invention is a compound of formula (I) wherein the compound's measured IC_{50} to the ORL-1 receptor is less than or equal to about 100 nM, preferably less than or equal to about 50 nM. In another embodiment of the present invention is a compound of formula (I) wherein the compound's measured Ki to the ORL-1 receptor is less than or equal to about 100 nM, preferably less than or equal to about 50 nM.

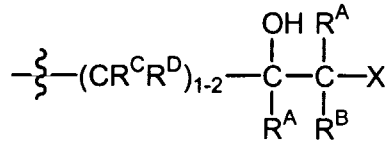
In an embodiment of the present invention R^0 is



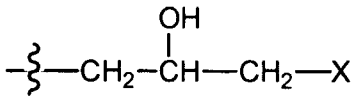
. In another embodiment of the present invention, R^0 is



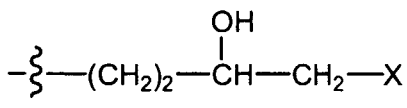
. In yet another embodiment of the present invention, R^0 is



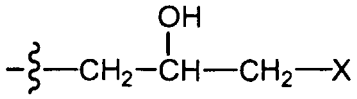
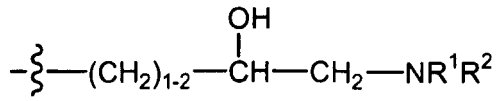
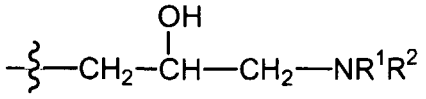
. Preferably, R^0 is selected from the group consisting of

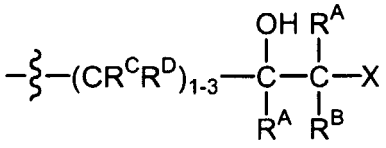
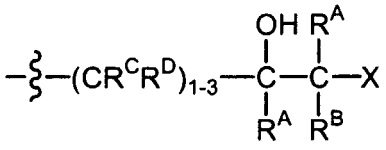


and



. More preferably, R^0 is


. In yet another embodiment of the present invention, R^0 is 
. Preferably, R^0 is 
.

In an embodiment of the present invention, the hydroxy group on the 
group is present in the R stereo-configuration. In another embodiment of the present invention, the hydroxy group on the 
group is present in the S stereo-configuration.

In an embodiment of the present invention R^A and R^B are each independently selected from hydrogen, methyl and ethyl, preferably R^A and R^B are each hydrogen. In another embodiment of the present invention R^C and R^D are each independently selected from hydrogen and C_{1-4}alkyl, preferably R^C and R^D are each hydrogen. In yet another embodiment of the present invention R^E is selected from the group consisting of hydrogen, methyl and ethyl, preferably R^E is hydrogen.

In an embodiment of the present invention X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SO-R^1$, $-SO_2-R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$, $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{1-4}alkyl)-NR^1-C(O)O-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one to two substituents independently selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxycarbonyl or carboxy. Preferably, X is selected from the group

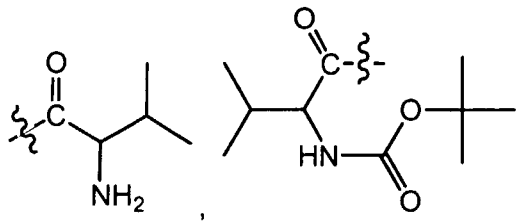
consisting of $-NR^1R^2$, $-OR^1$, $-SR^1$, $-S-(C_{2-4}alkyl)-NR^1-C(O)O-C(CH_3)_3$, $-S-(C_{2-4}alkyl)-NR^1R^2$ wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$ or $-S-(C_{2-4}alkyl)-NR^1-C(O)O-C(CH_3)_3$ group is optionally substituted with a carboxy or C_{1-4}alkoxycarbonyl group. More preferably, X is selected from the group consisting of $-NR^1R^2$, $-OR^1$, $-SR^1$, $-S-CH_2CH(CO_2H)-NH-C(O)-CH_3$ and $-S-CH_2CH(CO_2H)-NH-C(O)O-C(CH_3)_3$. More preferably still, X is selected from the group consisting of $-NR^1R^2$, $-SR^1$ and $-S-CH_2CH(CO_2H)-NH-C(O)-CH_3$.

In an embodiment of the present invention R^1 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, heteroaryl, heteroaryl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, cycloalkyl-alkyl, $C(O)-C_{1-4}$alkyl and -C(O)-heteroaryl; wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}$alkyl, $N(R^E)-C(O)OC(CH_3)_3$, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C_{1-4}alkylthio. Preferably, In an embodiment of the present invention R^1 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, heteroaryl, heteroaryl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, cycloalkyl-alkyl, $C(O)-C_{1-4}$alkyl and -C(O)-heteroaryl; wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}$alkyl, $N(R^E)-C(O)OC(CH_3)_3$, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C_{1-4}alkylthio.

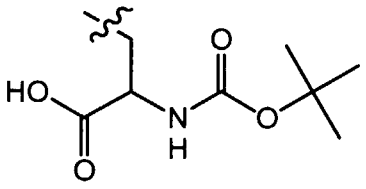
In another embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, C_{1-4}alkyl, arC_{1-4}alkyl, C_{1-4}alkoxycarbonyl and $C(O)-C_{1-4}$alkyl; wherein the C_{1-4}alkyl, arC_{1-4}alkyl or aryl group, whether alone or part of a substituent group, is optionally substituted with one to two substituents independently selected from carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl,

$N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl or $N(R^E)$-$C(O)OC(CH_3)_3$. Preferably, R^1 is selected from the group consisting of hydrogen, C_{1-4}alkyl, arC_{1-4}alkyl and $C(O)$-C_{1-4}alkyl; wherein the C_{1-4}alkyl, arC_{1-4}alkyl or aryl group, whether alone or part of a substituent group, is optionally substituted with one to two substituents independently selected from carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl or $N(R^E)$-$C(O)OC(CH_3)_3$.

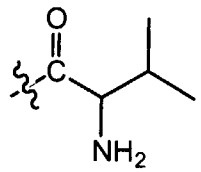
In another embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, amino-n-propyl, dimethylaminoethyl, benzyl, phenylethyl, 4-methyl-benzyl,



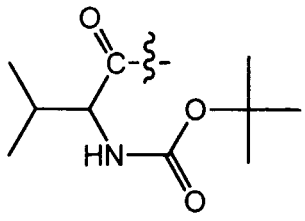
, 2-(3,4-dimethoxy-phenyl)ethyl, 3-methylphenyl, 2-amino-2-methoxycarbonyl-ethyl, ethoxy-carbonyl-methyl, t-butoxycarbonyl, and

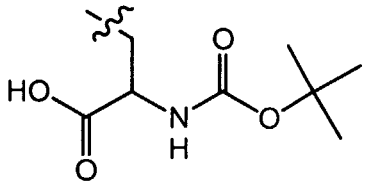


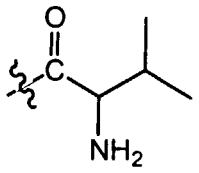
. Preferably, R^1 is selected from the group consisting of hydrogen, methyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, 4-methyl-benzyl,

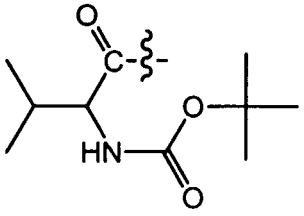


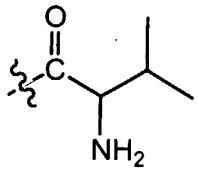
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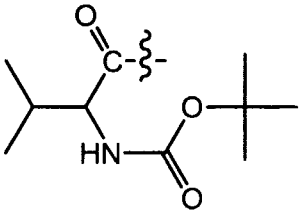


, 2-(3,4-dimethoxy-phenyl)ethyl, 3-methylphenyl, 2-amino-2-methoxycarbonyl-ethyl and .

In another embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, phenylethyl, ,

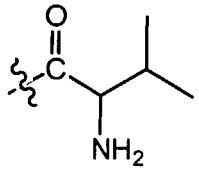


, 3-methyl-phenyl, 2-(3,4-dimethoxyphenyl)-ethyl, ethoxy-carbonyl-methyl, dimethylamino-ethyl and 2-amino-2-methoxycarbonyl-ethyl. Preferably, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, ,

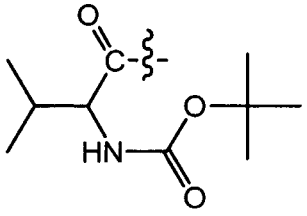


, 3-methyl-phenyl and 2-amino-2-methoxycarbonyl-ethyl.

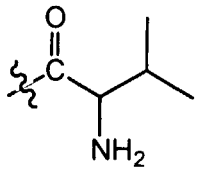
In yet another embodiment of the present invention, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, phenylethyl, 2-(3,4-dimethoxyphenyl)-ethyl,



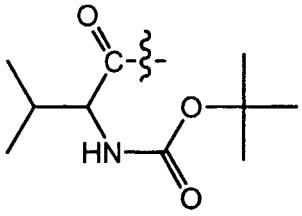
dimethylamino-ethyl, ethoxy-carbonyl-methyl, and



. Preferably, R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl,



and



.

In another embodiment of the present invention R^1 is selected from the group consisting of hydrogen, t-butoxycarbonyl, 2-(3,4-dimethoxyphenyl)-ethyl, 1-(3,4-dimethoxyphenyl)-n-ethyl and amino-n-propyl. In yet another embodiment of the present invention R^1 is selected from the group consisting of hydrogen, t-butoxycarbonyl and amino-n-propyl.

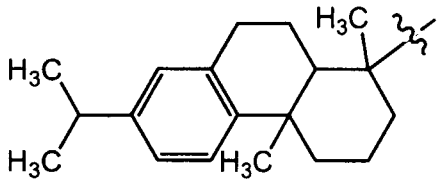
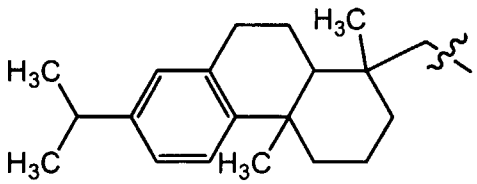
In an embodiment of the present invention R^2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, cycloalkyl, cycloalkyl-C_{1-4}alkyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, partially unsaturated carbocyclyl, partically unsaturated carbocyclyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-aryl, -C(O)-arC_{1-4}alkyl, -C(O)-heteroaryl,–C(O)-heterocycloalkyl, -C(O)O-cycloalkyl and –C(OO)-C_{1-4}alkyl; wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl, partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three

substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl, $(CH_3)_3COC(O)$-$N(R^E)$-C_{1-4}-alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl substituted heteroaryl-aminosulfonyl, -C(O)-C_{1-4}alkyl or C_{1-4}alkylthio. Preferably, R^2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, cycloalkyl-C_{1-4}alkyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, partially unsaturated carbocyclyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-aryl, -C(O)-arC_{1-4}alkyl, -C(O)-heteroaryl and –C(O)-heterocycloalkyl; wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl, partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl substituted heteroaryl-aminosulfonyl, -C(O)-C_{1-4}alkyl or C_{1-4}alkylthio.

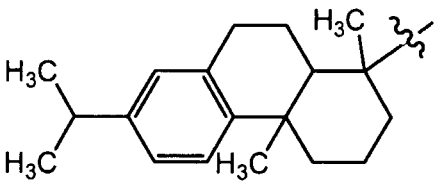
In an embodiment of the present invention, R^2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, cycloalkyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, partially unsaturated carbocyclyl, partially unsaturated carbocyclyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, cycloalkyl-C_{1-4}alkyl, -C(O)arC_{1-4}alkyl, -C(O)-heteroaryl, -C(OO)-cycloalkyl and –C(O)O-C_{1-4}alkyl; wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl, partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl, $(CH_3)_3CO$-C(O)-$N(R^E)$-C_{1-4}alkyl, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C_{1-4}alkylthio. Preferably, R^2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, partially unsaturated carbocyclyl, heteroaryl, heteroaryl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, cycloalkyl-alkyl and -C(O)-heteroaryl; wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl,

partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C_{1-4}alkylthio.

In an embodiment of the present invention, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, carboxy-methyl, ethoxycarbonylmethyl, 2,2,2,-triluoroethyl, ethoxy, dimethylaminoethyl, t-butoxycarbonylamino-ethyl, n-butyl, t-butyl, n-propyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, di(n-butyl)amino-n-propyl, t-butoxycarbonylamino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, t-butoxycarbonyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 3,4-dimethoxyphenyl, 2-aminophenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-cyclohexylphenyl, 4-(aminoethyl)phenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, -CH(CH_3)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl), 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)benzyl, 4-(dimethylamino)benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, (2,5-dimethoxy-2,5-dihydro-fur-2-yl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-

methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 6-methylthio-2-pyridyl-carbonyl, thienyl-methyl, 2-thienylethyl, 4-pyridinyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 1-phenyl-2-(t-butoxycarbonyl)ethyl, -C(O)-$C(OCH_3)(CF_3)$-phenyl, -C(O)O-(2-isopropyl-5-methyl-cyclohexyl), 1-(4-ethoxycarbonyl-piperidinyl), 2-(3H-imidazol4-yl)ethyl, 2-(1,2,3,4-tetrahydro-isoquinolinyl), 2-furyl-methyl, , , 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl, 2-(2-pyridyl)-ethyl, 2-(6-fluoro-2-indolyl)ethyl and 2-phenyl-cyclopropyl. Preferably, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, carboxy-methyl, ethoxycarbonylmethyl, 2,2,2,-triluoroethyl, ethoxy, dimethylaminoethyl, n-butyl, t-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, phenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-cyclohexylphenyl, 4-(aminoethyl)phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl), 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)benzyl, 4-(dimethylamino)benzyl, 2-

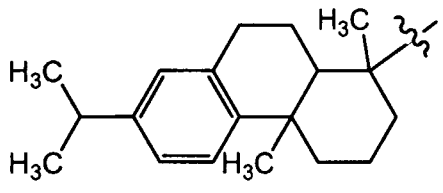
phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, (2,5-dimethoxy-2,5-dihydro-fur-2-yl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 6-methylthio-2-pyridyl-carbonyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 1-phenyl-2-(t-butoxycarbonyl)ethyl, 2-(1,2,3,4-tetrahydro-isoquinolinyl), 2-furyl-methyl,



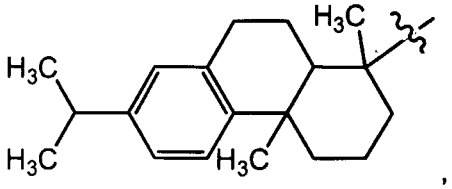
, 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl, 2-(2-pyridyl)-ethyl, 2-(6-fluoro-2-indolyl)ethyl and 2-phenyl-cyclopropyl.

In an embodiment of the present invention, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, 2,2,2-triluoroethyl, ethoxy, dimethylaminoethyl, n-butyl, t-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 2-aminophenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, 3,4-dimethoxyphenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-

dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), thienylmethyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-

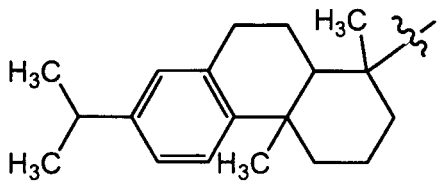


methyl, , 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl and 2-(6-fluoro-2-indolyl)-ethyl. Preferably still, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, 2,2,2-triluoroethyl, ethoxy, dimethylaminoethyl, n-butyl, t-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, phenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-

morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-methyl, , 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl and 2-(6-fluoro-2-indolyl)-ethyl.

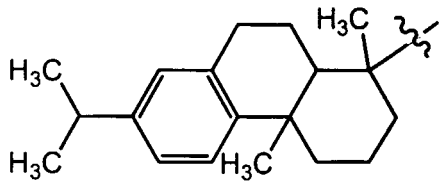
In an embodiment of the present invention, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, ethoxy, dimethylaminoethyl, n-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 2-aminophenyl, 3,4-dimethoxyphenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-

adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), thienylmethyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-



methyl, , 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl and 2-phenoxy-ethyl. Preferably, R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, ethoxy, dimethylaminoethyl, n-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxv, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 2-thienylethyl, 1-naphthyl,

1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-



methylenedioxyphenyl)ethyl, 2-furyl-methyl, 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl and 2-phenoxy-ethyl.

In an embodiment of the present invention R^2 is selected from the group consisting of hydrogen, methyl, n-butyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, t-butoxycarbonylamino-n-propyl, N-methyl-N-t-butoxycarbonyl-amino-n-ethyl, 3-nitrobenzyl, 4-methoxycarbonyl-benzyl, -CH(CH_3)-phenyl, 4-pyridinyl, 1-(4-ethoxycarbonyl-piperidinyl) and 2-(3H-imidazol-4-yl)-ethyl.

Preferably, R^2 is selected from the group consisting of hydrogen, methyl, n-butyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, N-methyl-N-t-butoxycarbonyl-amino-n-ethyl, 3-nitrobenzyl, 4-methoxycarbonyl-benzyl, -CH(CH_3)-phenyl, 4-pyridinyl and 2-(3H-imidazol-4-yl)-ethyl.

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, hydroxy substituted C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, phenyl, arC_{1-4}alkyl, heterocycloalkyl, di(C_{1-4}alkyl)amino-carbonyl, C_{1-4}alkoxycarbonylamino or phenylamino-C_{1-4}alkyl; wherein the phenyl or arC_{1-4}alkyl substituent on the heteroaryl or heterocycloalkyl group is optionally substituted with one or two substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$ or substituted

phenyl; wherein the substituents on the phenyl are one to three independently selected from halogen. Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, phenyl, arC_{1-4}alkyl, heterocycloalkyl, di(C_{1-4}alkyl)amino-carbonyl, or phenylamino-C_{1-4}alkyl; wherein the phenyl or arC_{1-4}alkyl substituent on the heteroaryl or heterocycloalkyl group is optionally substituted with one or two substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$ or substituted phenyl; wherein the substituents on the phenyl are one to three independently selected from halogen.

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from heterocycloalkyl and heteroaryl; wherein the heteroaryl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4}alkyl, hydroxy substituted C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, arC_{1-4}alkyl, heterocycloalkyl, C_{1-4}alkoxycarbonyl, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)amino-carbonyl, t-butoxycarbonyl, t-butoxycarbonylamino or phenylamino-C_{1-4}alkyl; wherein the phenyl or arC_{1-4}alkyl substituent is optionally substituted with one or two substituents independently selected from chloro, trifluoromethyl or chlorophenyl. Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from heterocycloalkyl and heteroaryl; wherein the heteroaryl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, arC_{1-4}alkyl, heterocycloalkyl, C_{1-4}alkoxycarbonyl, di(C_{1-4}alkyl)amino-carbonylor phenylamino-C_{1-4}alkyl; wherein the phenyl or arC_{1-4}alkyl substituent is

optionally substituted with one or two substituents independently selected from trifluoromethyl or chlorophenyl.

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-morpholinyl, 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-pyrrolidinyl-piperidinyl), 1-(4-phenyl-piperidinyl), 1-(3-hydroxy-piperidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3,5-dimethyl-piperidinyl), 1-(4-dimethylamino-piperidinyl), 1-(4-(3,4-methylenedioxyphenylmethyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-t-butoxycarbonylamino-piperidinyl), 1-(2,3-dihydro-1H-pyrrolyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-pyrrolidinyl, 1-(2,3,-dihydro-pyrrolidinyl), 1-(3-hydroxy-pyrrolidinyl), 1-(3-(S)-hydroxy-pyrrolidinyl), 1-piperidinyl, 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-ethoxycarbonyl-piperidinyl), 1-imidazolyl, 1-(2-(phenylamino-methyl)-N-pyrrolidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(3,4-dihydroxy-2,5-bis-hydrooxymethyl-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-methylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino)-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl). Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenylmethyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(2,3-dihydro-1H-pyrrolyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-pyrrolidinyl, 1-piperidinyl, 1-(4-

ethoxycarbonyl-piperidinyl), 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl).

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-phenyl-piperidinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperiazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-morpholinyl, 1-pyrrolidinyl, 1-(2,3-dihydro-pyrrolidinyl), 1-piperidinyl, 1-(3,5-dimethyl-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-(ethoxycarbonyl)-piperidinyl), 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl). Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperiazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-pyrrolidinyl, 1-piperidinyl, 1-(4-(ethoxycarbonyl)-piperidinyl), 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl).

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-phenyl-piperidinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperiazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-

piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-(3,5-dimethyl-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-(ethoxycarbonyl)-piperidinyl), 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, 1-imidazolyl, 1-(2,3-dihydro-pyrrolidinyl), and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl). Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperiazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-(4-(ethoxycarbonyl)-piperidinyl), 1-piperidinyl, 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl).

In an embodiment of the present invention, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 1-pyrrolidinyl, 1-(3-hydroxy-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(4-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(4-dimethylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl).

Preferably, when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 1-pyrrolidinyl, 1-(3-hydroxy-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-(R)-

dimethylamino-pyrrolidinyl), 1-(4-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(S)-methylamino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(4-dimethylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl).

In an embodiment of the present invention, n is an integer from 0 to 1, preferably n is 0. In an embodiment of the present invention m is 0. In another embodiment of the present invention m is 1.

In an embodiment of the present invention p is an integer from 0 to 2, preferably p is an integer from 0 to 1. In an embodiment of the present invention q is 0. In another embodiment of the present invention, q is 1.

In an embodiment of the present invention, R^3 is selected from the group consisting of aryl and arC_{1-4}alkyl; wherein the aryl or arC_{1-4}alkyl group is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$. Preferably, R^3 is aryl; wherein the aryl group is optionally substituted with one or more substituents independently selected from halogen. More preferably, R^3 is selected from the group consisting of phenyl and 4-fluorophenyl.

In an embodiment of the present invention, L^1 is C_{1-4}alkyl; wherein the C_{1-4}alkyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-4}alkyl, fluorinated C_{1-4}alkyl or C_{1-4}alkoxy. Preferably, L^1 is unsubstituted C_{1-4}alkyl. More preferably, L^1 is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$ and $-CH_2CH_2-$. More preferably still, L^1 is $-CH_2-$ or $-CH_2CH_2-$;

In an embodiment of the present invention,  is selected from the group consisting of partially unsaturated carbocyclyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl.

In another embodiment of the present invention,  is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphthyl, 2-thienyl, benzothienyl, 4,5,6,7-tetrahydro-benzothienyl, bicyclo[3.1.1]hepten-2-yl, bicyclo[3.1.1]heptyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl. Preferably,  is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl, 2-naphthyl, 2-thienyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl.

In another embodiment of the present invention,  is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl and (3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-2-yl.

In another embodiment of the present invention,  is selected from the group consisting of cyclooctyl, 1-naphthyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, bicyclo[3.1.1]hepten-2-yl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl.

In an embodiment of the present invention, R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO-$N(R^E)_2$, -SO_2- $N(R^E)_2$ and -C(O)- $N(R^E)_2$.

In another embodiment of the present invention, R^5 is selected from the group consisting of halogen, C_{1-4}alkyl and trifluoromethyl. Preferably, R^5 is selected from the group consisting of chloro, methyl, n-propyl and trifluoromethyl.

In another embodiment of the present invention, R^5 is selected from the group consisting of methyl, n-propyl, chloro and trifluoromethyl. Preferably, R^5 is selected from the group consisting of methyl, n-propyl and trifluoromethyl. More preferably, R^5 is selected from the group consisting of methyl and n-propyl. In yet another embodiment of the present invention, R^5 is methyl.

In an embodiment of the present invention R^6 is $-(L^2)_0-R^7$. In another embodiment of the present invention, R^6 is $-(L^2)_1-R^7$ and L^2 is selected from the group consisting of $-C_{1-4}$alkyl-, -O-, -S-, $-N(R^E)-$, -C(O)O- and -O-C(O)-.

In an embodiment of the present invention, R^7 is selected from the group consisting of cycloalkyl, aryl, heteroaryl and heterocycloalkyl; wherein the aryl, heteroaryl or heterocycloalkyl group is optionally substituted with one to two substituents independently selected from hydroxy, carboxy, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy or C_{1-4}alkoxycarbonyl. Preferably, R^7 is selected from the group consisting of aryl and heteroaryl. More preferably, R^7 is selected from the group consisting of phenyl and 2-thienyl. More preferably still, R^7 is 2-thienyl.

In an embodiment of the present invention is a compound of formula (I) selected from the group consisting of

8-(R) acenaphthen-1-yl-3-(3-amino-2-(S)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R) acenaphthen-1-yl-3-(3-amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R)-Acenaphthen-1-yl-3-(3-dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R)-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxymethyl-piperidin-1-yl)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-8-cyclooctyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-1-(S)-(3aS)-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-1,3,8-triaza-spiro[4.5]decan-4-one;

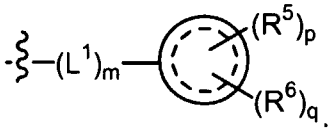
1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxy-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-methylamino-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-[3-(3-Dimethylamino-propylamino)-2-(R)-hydroxy-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

and pharmaceutically acceptable salts thereof.

With regard to compounds of formula (E), in an embodiment of the present invention Y is selected from the group consisting of hydrogen, C_{1-4}alkyl and t-butoxycarbonyl, preferably, C_{1-4}alkyl or t-butoxycarbonyl, more preferably ethyl. In another embodiment of the present invention Y is



Additional embodiments of the present invention, include those wherein the substituents selected for one or more of the variables defined herein (i.e. R^0, R^3, n, R^4, m, L^1, , p, R^5, q, R^6 and Y) are independently selected to be any individual substituent or any subset of substituents selected from the complete list as defined herein.

As used herein, unless otherwise noted, "halogen" shall mean chlorine, bromine, fluorine and iodine.

As used herein, the term "alkyl", whether used alone or as part of a substituent group, include straight and branched alkyl chain, preferably comprising one to eight carbon atoms. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, t-butyl, pentyl and the like. As used herein, the term "lower alkyl" shall mean a straight or branched alkyl chain comprising one to four carbon atoms. Suitable examples of a lower alkyl group include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like.

As used herein, unless otherwise noted, the term "hydroxy substituted alkyl" shall mean any straight or branched alkyl chain which is substituted with one or more hydroxy groups, for example hydroxymethyl, 1-hydroxy-eth-2-yl, and the like. Preferably, the alkyl chain is substituted with one to three hydroxy groups, more prefereably one hydroxy group.

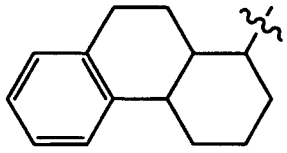
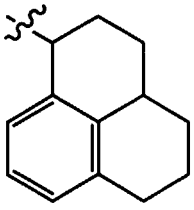
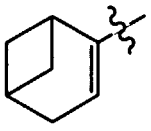
As used herein, unless otherwise noted, "alkoxy" shall denote an oxygen ether radical of the above described straight or branched chain alkyl groups. For example, methoxy, ethoxy, n-propoxy, sec-butoxy, t-butoxy, n-hexyloxy and the like.

As used herein, unless otherwise noted, "aryl" shall refer to unsubstituted carbocylic aromatic groups such as phenyl, naphthyl, and the like.

As used herein, unless otherwise noted, "arC_{1-4}alkyl" shall mean any lower alkyl group (i.e. C_{1-4}alkyl group) substituted with an aryl group such as phenyl, naphthyl and the like. Suitable examples of an arC_{1-4}alkyl group include, benzyl, 2-phenylethyl (i.e. Phenyl-CH_2-CH_2-), 3-phenyl-n-propyl (i.e. Phenyl-CH_2-CH_2-CH_2-), naphthyl-methyl, and the like.

As used herein, unless otherwise noted, the term "acyl" shall mean a radical formed from an organic acid by removal of the hydroxy group. Suitable example include acetyl, benzoyl, and the like.

As used herein, unless otherwise noted, the term "cycloalkyl" shall mean any stable three to fourteen membered monocyclic, bicyclic, tricyclic or bridged carbon based, saturated ring system, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantanyl, bicyclo[3.1.1]heptyl, and the like.

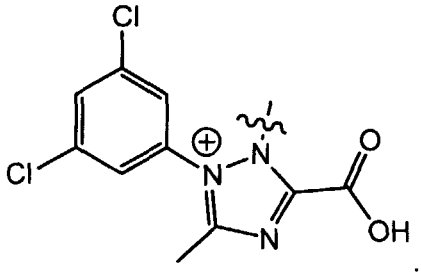
As used herein, unless otherwise noted, the term "carbocyclyl" shall mean four to fourteen membered, preferably five to thirteen membered, more preferably five to ten membered monocyclic, bicyclic or tricyclic, carbon based ring structure. Similarly, unless otherwise noted, the term "partially unsaturated carbocyclyl" shall mean any five to fourteen, preferably five to thirteen, more preferably five to ten, membered monocyclic, bicyclic or tricyclic, carbon based ring structure containing at least one unsaturated (double or triple) bond. Suitable examples of partially unsaturated carbocyclyl groups include 1,2,3,4-tetrahydronaphthyl, cyclohexen-1-yl, 1-acenaphthenyl, , , , and the like.

As used herein, unless otherwise noted, "heteroaryl" shall denote any five to seven, preferably five to six, membered monocyclic aromatic ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to three additional heteroatoms independently selected from the group consisting of O, N and S; or a nine to ten membered bicyclic aromatic ring structure containing at least one heteroatom selected from

the group consisting of O, N and S, optionally containing one to four additional heteroatoms independently selected from the group consisting of O, N and S. The heteroaryl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure.

Examples of suitable heteroaryl groups include, but are not limited to, pyrrolyl, furyl, thienyl, oxazolyl, imidazolyl, pyrazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furazanyl, indolizinyl, indolyl, isoindolinyl, indazolyl, benzofuryl, benzothienyl, benzimidazolyl, benzthiazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, isothiazolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, and the like. Preferred heteroaryl groups include thienyl, pyridyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, indolyl and quinolinyl.

One skilled in the art will recognize that wherein the heteroaryl group contains one or more nitrogen atoms, said heteroaryl group may optionally be present as or within a substituent group in a quaternary form, for example as in 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl), a substituent of the formula

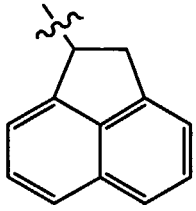
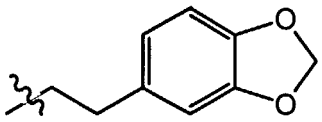
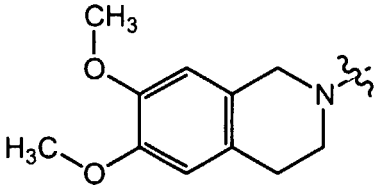
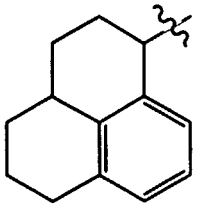


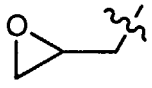
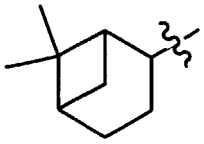
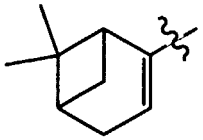
.

As used herein, the term "heterocycloalkyl" shall denote any five to seven, preferably five to six, membered monocyclic, saturated or partially unsaturated ring structure containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to three additional heteroatoms independently selected from the group consisting of O, N and S; or a nine to ten membered saturated, partially unsaturated or partially aromatic bicyclic ring system containing at least one heteroatom selected from the group consisting of O, N and S, optionally containing one to four additional heteroatoms independently selected from the group consisting of O, N and S. The

heterocycloalkyl group may be attached at any heteroatom or carbon atom of the ring such that the result is a stable structure.

Examples of suitable heterocycloalkyl groups include, but are not limited to, pyrrolinyl, pyrrolidinyl, dioxalanyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, trithianyl, indolinyl, chromenyl, 3,4-methylenedioxyphenyl, 2,3-dihydrobenzofuryl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4-tetrahydroquinolinyl, 4,5,6,7-tetrahydro-benzo[b]thienyl and the like. Preferred heterocycloalkyl groups include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,2,3,4-tetrahydroisoquinolinyl, 4,5,6,7-tetrahydro-benzo[b]thienyl, 3,4-methylenedioxyphenyl and 3,4-dihydro-2H-benzo[b][1,4]dioxepine.

As used herein, the name "1-acenaphthenyl" shall mean a substituent group of the formula . As used herein, the name "2-(3,4-methylenedioxyphenyl)ethyl" shall mean a substituent group of the formula . As used herein, the name "2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)" shall mean a substituent group of the formula . As used herein, the name "2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl shall mean a substituent group of the formula . As used herein, the name "oxarinyl-methyl" shall

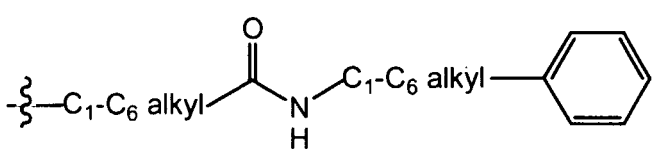
mean a substituent group of the formula  . As used herein, the name "6,6-dimethyl-bicyclo[3.1.1]heptyl" shall mean a substituent group of the formula  . As used herein, the name "6,6-dimethyl-bicyclo[3.1.1]hept-2-enyl" shall mean a substituent group of the formula  .

As used herein, the notation "*" shall denote the presence of a stereogenic center.

When a particular group is "substituted" (e.g., alkyl, aryl, carbocyclyl, heterocycloalkyl, heteroaryl), that group may have one or more substituents, preferably from one to five substituents, more preferably from one to three substituents, most preferably from one to two substituents, independently selected from the list of substituents.

With reference to substituents, the term "independently" means that when more than one of such substituents is possible, such substituents may be the same or different from each other.

Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first, followed by the adjacent functionality toward the point of attachment. Thus, for example, a "phenylC_1-C_6alkylaminocarbonylC_1-C_6alkyl" substituent refers to a group of the formula



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

AcCN	=	Acetonitrile
BINAP	=	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	=	t-Butoxycarbonyl
CBz	=	benzyloxycarbonyl (C_6H_5-CH_2-O-C(O)-)
DAMGO	=	Tyr-D-Ala-Gly-N-methyl-Phe-Gly-ol
DCC	=	N,N-dicyclohexylcarbodiimide
DCE	=	Dichloroethane
DCM	=	Dichloromethane
DIPEA or DIEA	=	Diisopropylethylamine
DMF	=	N,N-Dimethylformamide
DME	=	1,2-dimethoxyethane
DMSO	=	Dimethylsulfoxide
DPDPE	=	Tyr-D-Pen-Gly-p-Chloro-Phe-D-Pen[Disulfide Bridge: 2-5]
EDCI	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA	=	Ethylenediaminetetraacetic acid
EGTA	=	Ethylene glycol-O,O'-bis(2-aminoethyl)-N,N,N',N'-tetracacetic acid
EtOAc	=	Ethyl acetate
Fmoc	=	9-Fluorenylmethoxycarbonyl
HBTU	=	O-(1H-Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
hex	=	Hexane
HPLC	=	High Pressure Liquid Chromatography
KO-t-Bu	=	Potassium t-butoxide
LiHMDS	=	Lithium bis(trimethylsilyl)amide
mCPBA	=	meta-chloroperoxybenzoic acid
MeCN	=	Acetonitrile
Ms	=	mesyl or methanesulfonyl group

μW	=	Microwave
NaHMDS	=	Sodium bis(trimethylsilyl)amide
NatBuO or tBuONa	=	Sodium t-butoxide
NMP	=	N-methyl-2-pyrrolidinone
$Pd_2(dba)_3$	=	Tris(dibenzylideneacetone) dipalladium (0)
$Pd(OAc)_2$	=	Palladium (II) acetate
$Pd(PPh_3)_4$	=	tetrakis(triphenylphosphine)palladium(0)
$PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_2Cl_2$	=	di(chloro)di(triphenylphosphine)palladium(0)
$P(tBu)_3$	=	Tri-t-butyl phosphine
PEI	=	Polyethylimine
TEA or Et_3N	=	Triethylamine
TFA	=	Trifluoroacetic acid
THF	=	Tetrahydrofuran
TLC	=	Thin Layer Chromatography
TNE Buffer		50 mM Tris-HCl, pH 7.4+ 5 mM EDTA + 150 mM NaCl
Tris HCl	=	Tris[hydroxymethyl]aminomethyl hydrochloride
Ts	=	Tosyl or p-toluenesulfonyl group
U69593	=	(+)-(5α,7α,8β)-N-methyl-N-7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl] benzene acetamide

As used herein, unless otherwise noted, the term "eating disorders" shall mean any disorder associated with eating. Suitable examples include, but are not limited to anorexia nervosa, bulimia, binge eating, food cravings, and the like.

As used herein, unless otherwise noted, the term "adrenal disorders" shall mean disorders mediated by the adrenal gland. Suitable examples include, but are not limited to Cushing's syndrome, Addison's disease, and the like.

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

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

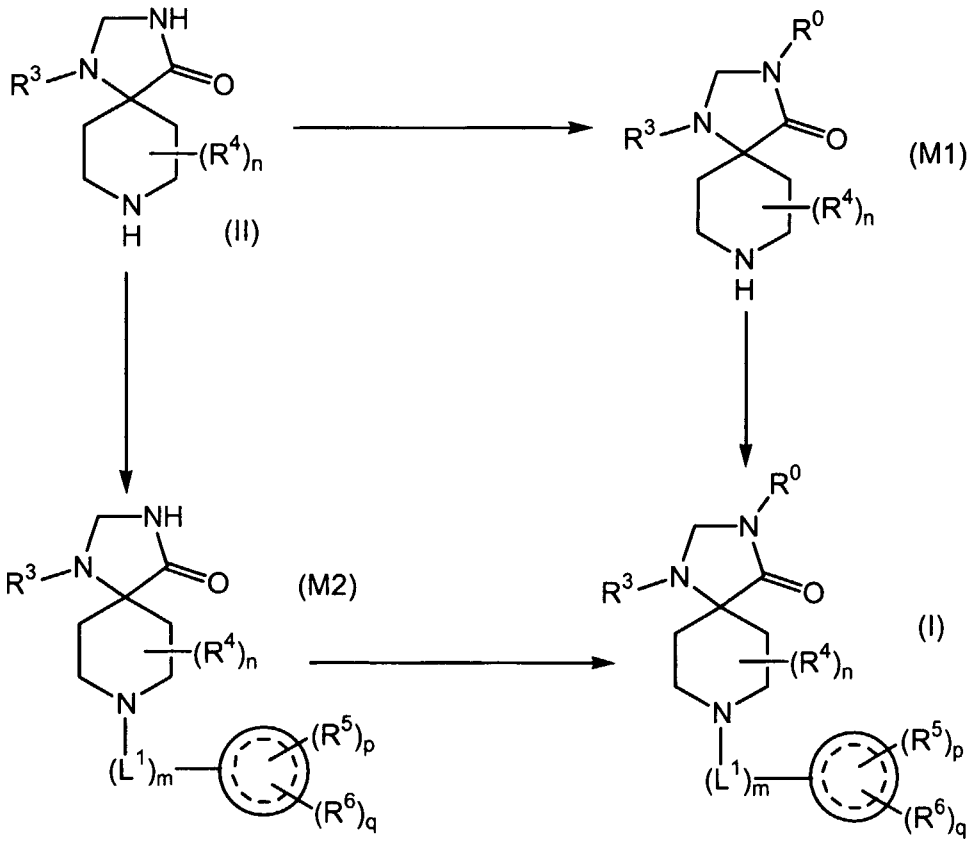
As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

For use in medicine, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." Other salts may, however, be useful in the preparation of compounds according to this invention or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. Thus, representative pharmaceutically acceptable salts include the following:

acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate,

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

The compounds of formula (I) of the present invention may be prepared according to the processes described in more detail herein. More particularly, the compounds of formula (I) may be prepared through intermediates of formula (M1) or (M2), as outlined in Scheme 1.



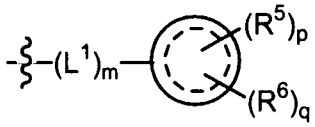
Scheme 1

More particularly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted to yield the compound of formula (M1), which is then further reacted to yield the corresponding compound of formula (I).

Alternatively, the compound of formula (II) is reacted to yield the corresponding compound of formula (M2), which is further reacted to yield the corresponding compound of formula (I).

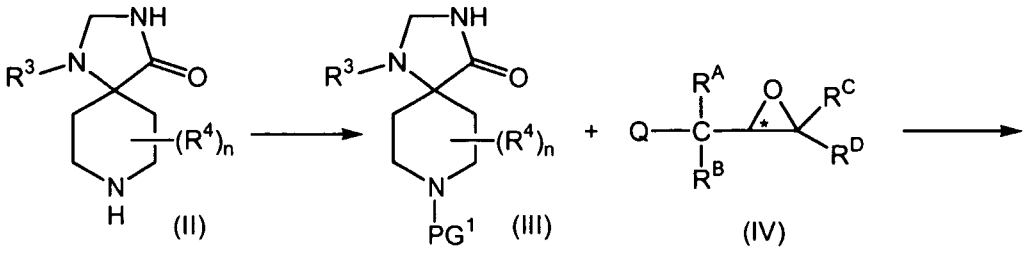
One skilled in the art will recognize that in the processes outlined above, more particularly in the reaction of a compound of formula (II) to form the compound of formula (M1), the N atom at the 8 position of the 1,3,8-triazaspiro[4.5]decan-4-one core is preferably protected, by known methods, with a known protecting group such as BOC, Fmoc, CBz, benzoyl, benzhydryl, and the like. One skilled in the art will further recognize that when a protecting group is utilized in the preparation of the compound of formula (M1), the protecting group is removed, by known methods, prior to reacting the compound of formula (M1) to yield the compound of formula (I).

One skilled in the art will recognize that the processes hereinafter outlined in Schemes 2 to 7 incorporate the R^0 or "top" substituent portion of the molecule onto the core structure, whereas Schemes 8 to 14 incorporate the

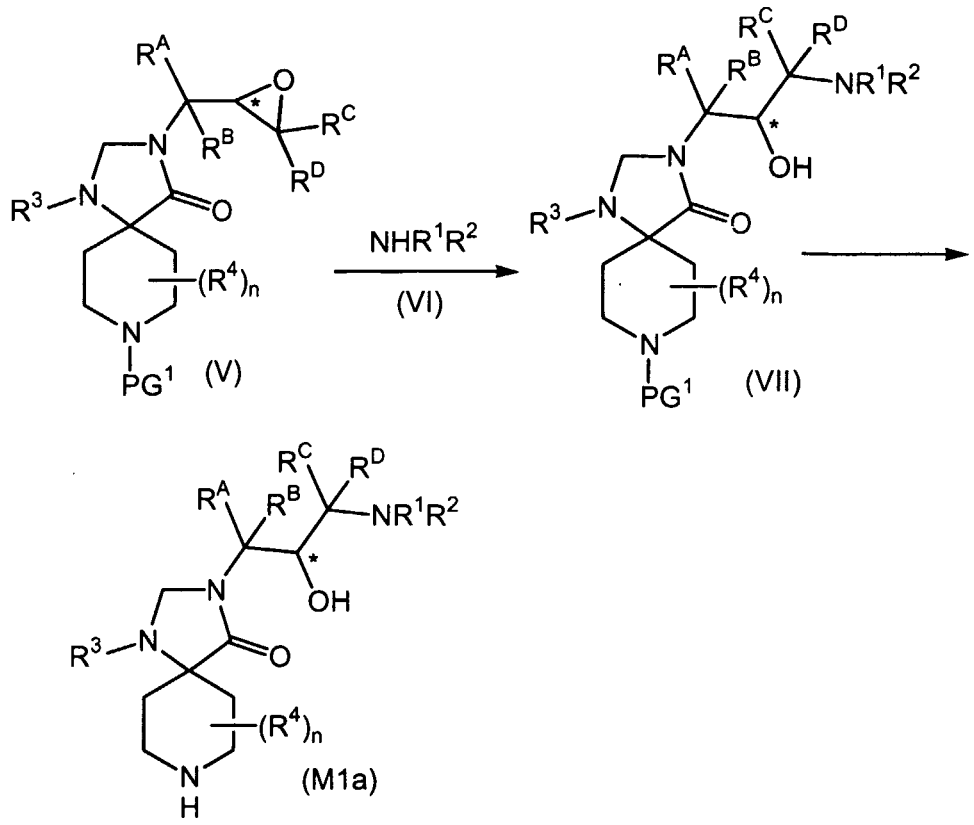


or "bottom" substituent portion of the molecule onto the core structure. One skilled in the art will further recognize that the top and bottom substituent portions may be incorporated into the compound of formula (I) in any order which yields the desired product.

Compounds of formula (M1) wherein R^0 is $-CR^AR^B-CH(OH)-CR^CR^D-X$ and X is NR^1R^2 may be prepared from a suitably substituted compound of formula (II) according to the process outlined in Scheme 2.



(II) (III) (IV)



Scheme 2

Accordingly, a suitably substituted compound of formula (II), is protected by known methods, with a suitably protecting group PG^1, such as t-butoxycarbonyl (BOC), CBz, Fmoc, benzhydryl, triphenylmethyl, 4-methoxybenzyl, benzoyl, and the like, to yield the corresponding compound of formula (III).

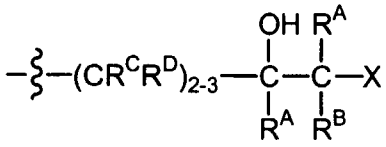
The compound of formula (III) is reacted with a suitable substituted compound of formula (IV) wherein Q is a suitable leaving group such as Cl, Br, I, tosylate, mesylate, and the like, a known compound or compound prepared by known methods, in the presence of a base such as NaH, KO-t-Bu, K_2CO_3, NaHMDS, LiHMDS, and the like, in an organic solvent such as NMP, DMF, THF, and the like, to yield the corresponding compound of formula (V).

The compound of formula (V) is reacted with a suitably substituted amine of formula (VI), a known compound or compound prepared by known methods, in an organic solvent such as ethanol, acetonitrile, methanol, isopropanol, and the like, to yield the corresponding compound of formula (VII).

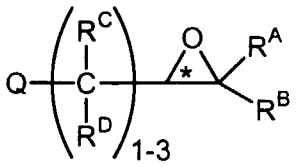
The compound of formula (VII) is de-protected by known methods, to yield the corresponding compound of formula (M1a).

One skilled in the art will recognize that in the preparation of compounds of formula (I) and (M1a) as in Scheme 2 above (i.e. in reactions where the oxarinyl group is opened with a suitably substituted compound of formula (VI)), the stereo-configuration of the hydroxy group will be determined by the stereo-configuration of the compound of formula (IV), with the naming (R or S) of the stereo-center based on chemical nomenclature rules. Thus, for example, wherein the process outlined in Scheme 2 above R^1, R^2, R^A, R^B, R^C and R^D are each hydrogen, the compound of formula (IV) is 2-(R)-chloromethyl-oxirane, then the compound of formula (M1a) will have the hydroxy group in the (R) position.

Compounds of formula (M1a) wherein R^0 is



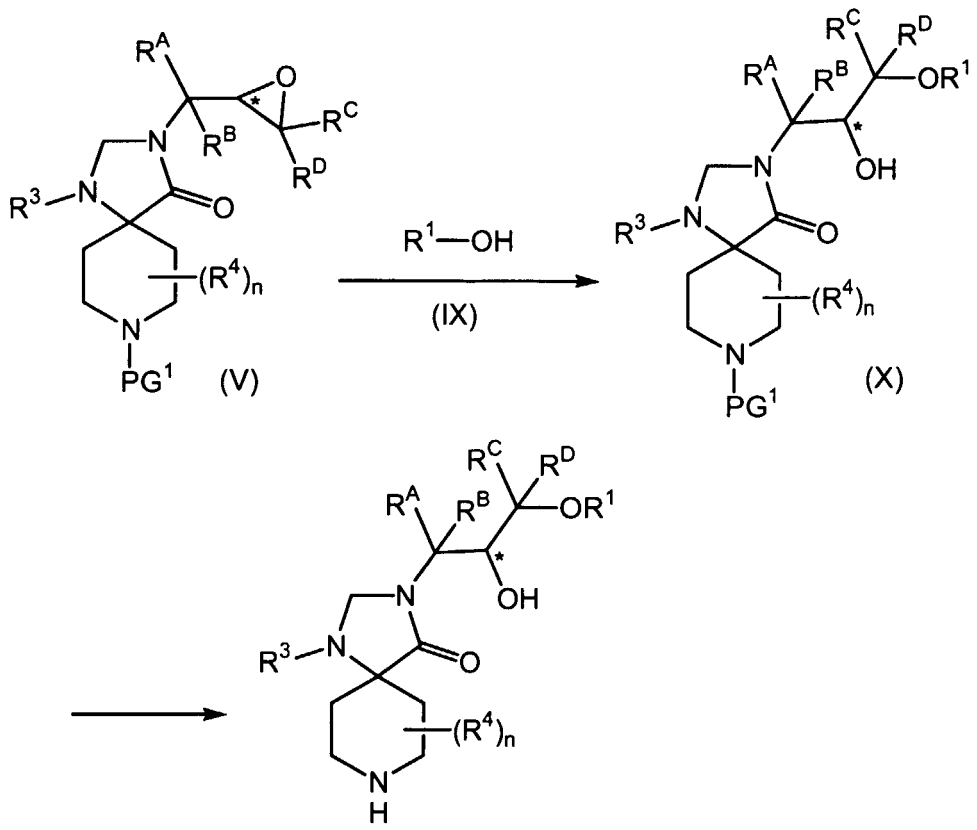
may be similarly prepared according to the process outlined in Scheme 2 above, with substitution of a suitably substituted compound of formula (VIII)



(VIII)

wherein Q is a suitable leaving group as previously defined, a known compound or compound prepared by known methods, for the compound (IV).

Compounds of formula (M1) wherein X is $-O-R^1$ may be prepared from a suitably substituted compound of formula (V) according to the process outlined in Scheme 3.

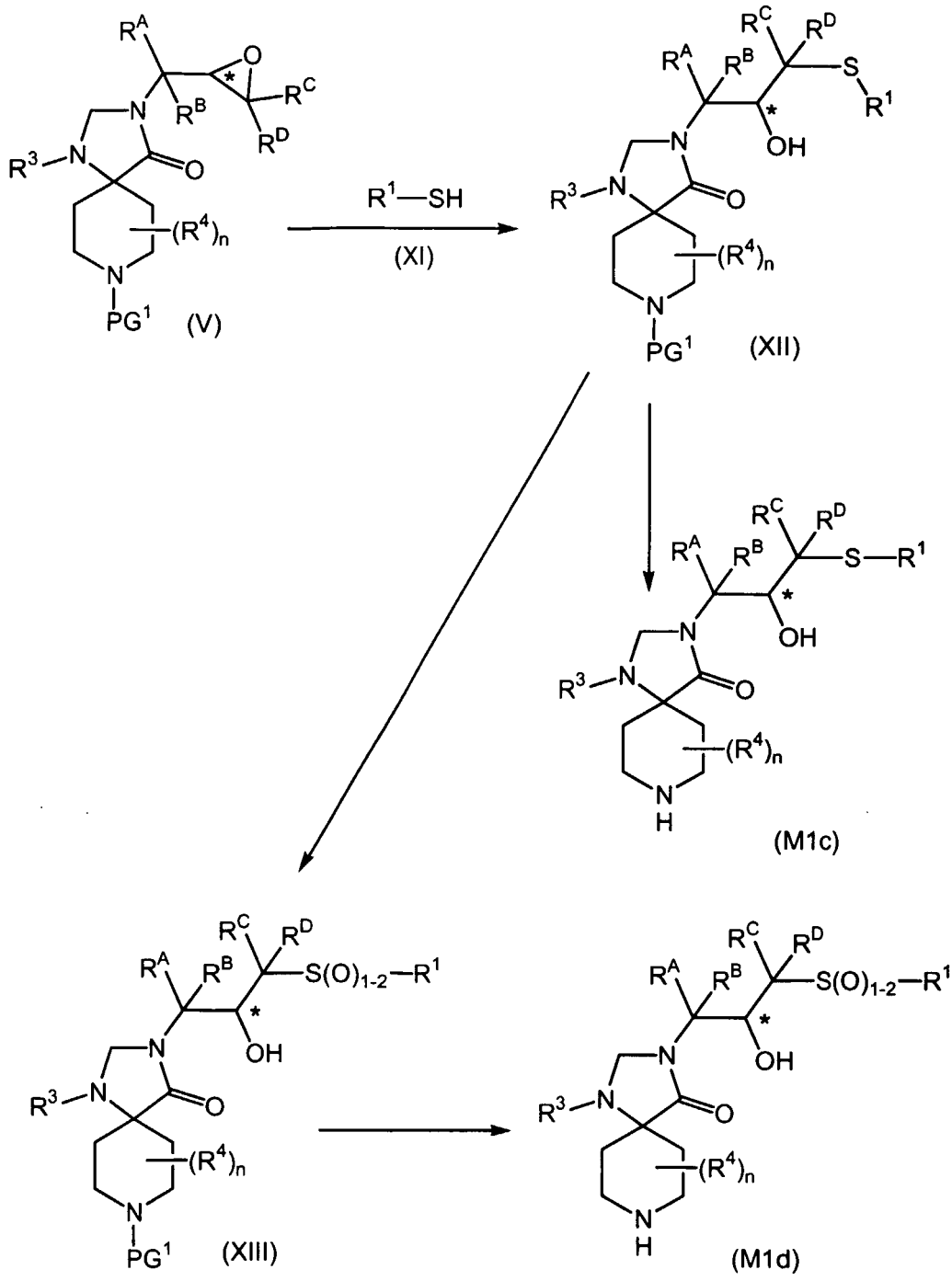


Scheme 3

Accordingly, a suitably substituted compound of formula (V), is reacted with suitably substituted compound of formula (IX), a known compound or compound prepared by known methods, in the presence of a base such as NaH, KH, sodium trimethylsilylamide, TEA, DIPEA, and the like, wherein the base is present in amount equal to or greater than about one molar equivalent, in an organic solvent such as THF, NMP, DMF, and the like, to yield the corresponding compound of formula (X).

The compound of formula (X) is de-protected, by known methods, to yield the corresponding compound of formula (M1b).

Compounds of formula (M1) wherein X is selected from the group consisting of -S-R^1, -SO-R^1 or -SO_2-R^1 may be prepared from a suitably substituted compound of formula (V) according to the process outlined in Scheme 4.



Scheme 4

Accordingly, a suitably substituted compound of formula (V) is reacted with a suitably substituted compound of formula (XI), a known compound or compound prepared by known methods, in the presence of a base such as TEA, DIPEA, and the like, in a protic solvent such as ethanol, methanol, NMP,

and the like, or a mixture thereof, preferably at an elevated temperature in the range of about room temperature to about 100°C, preferably at a temperature of about 50 to about 100°C, to yield the corresponding compound of formula (XII).

The compound of formula (XII) is de-protected by known methods, to yield the corresponding compound of formula (M1c), wherein X is $-S-R^1$.

Alternatively, the compound of formula (XII) is oxidized with an oxidizing agent such as hydrogen peroxide, mCPBA, and the like, according to known methods, to yield the corresponding compound of formula (XIII).

The compound of formula (XIII) is de-protected by known methods, to yield the corresponding compound of formula (M1d), wherein X is $-SO-R^1$ or $-SO_2-R^1$.

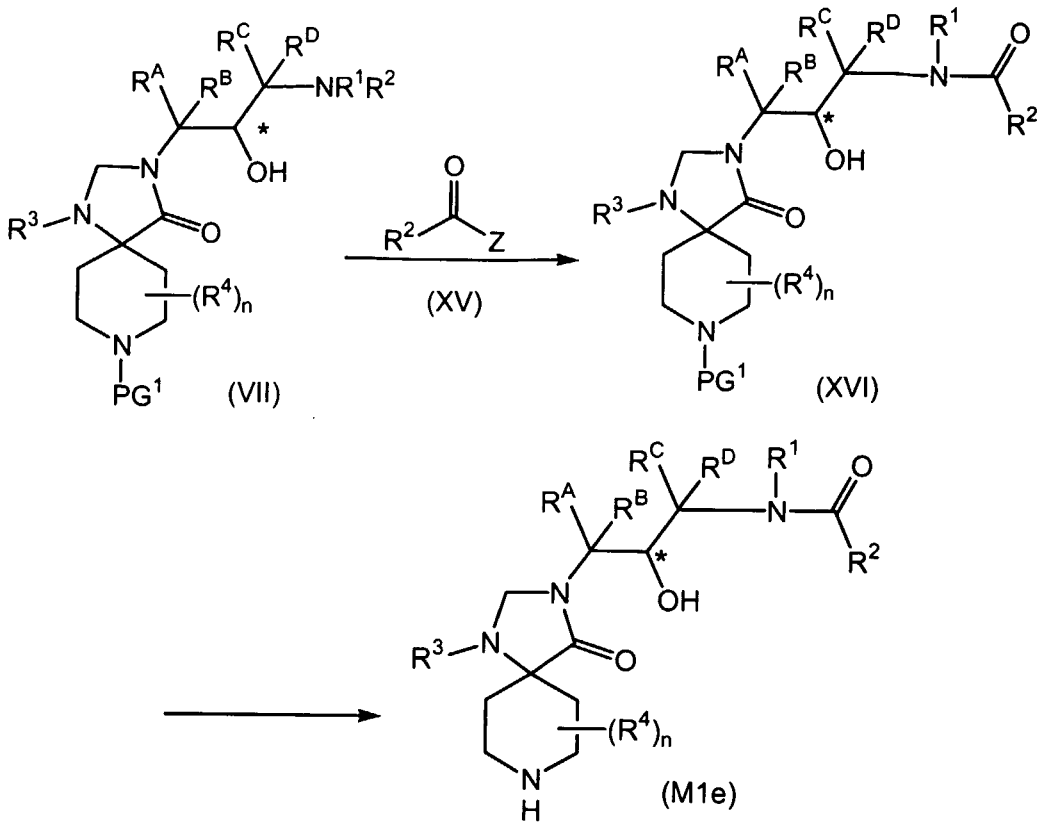
One skilled in the art will recognize that in the processes described in Scheme 4 above, the PG^1 protecting group on the N atom at the 8-position of the 1,3,8-triazaspiro[4.5]decan-4-one is not mandatory (but may be preferred), as the reactions will yield the desired compounds even in the absence of protection of the N atom.

One skilled in the art will recognize that compounds of formula (M1) wherein X is selected from $-S-(alkyl)-NR^1R^2$, $-SO-(alkyl)-NR^1R^2$ or $-SO_2-(alkyl)-NR^1R^2$ may be similarly prepared according to the process outlined in Scheme 4 above, with substitution of a suitably substituted compound of formula (XIV)

$$HS—(alkyl)—NR^1R^2 \qquad (XIV),$$

a known compound or compound prepared by known methods, for the compound of formula (XI).

Compounds of formula (M1) wherein X is $-NR^1-C(O)-R^2$ may be prepared according to the process outlined in Scheme 5.

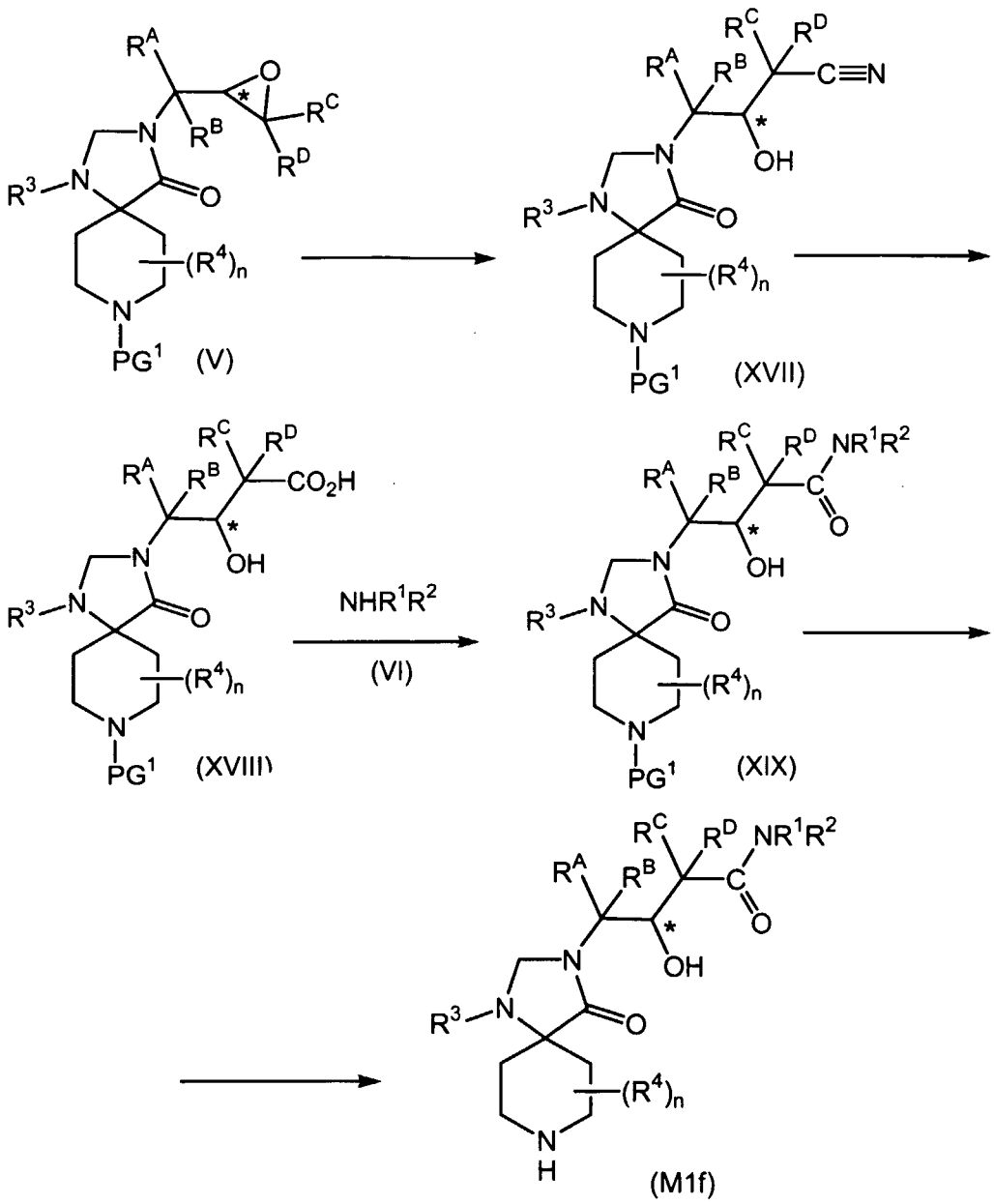


Scheme 5

Accordingly, a suitably substituted compound of formula (VII), wherein R^1 is hydrogen, is reacted with a suitably substituted compound of formula (XV), wherein Z is Cl, Br or OH, a known compound or compound prepared by known methods, in the presence of a base such as TEA, DIPEA, pyridine, and the like, wherein the base is present in an amount equal to or greater than about one molar equivalent, in an organic solvent such as THF, DMF, NMP, DCM, and the like, preferably at room temperature, to yield the corresponding compound of formula (XVI). Wherein the compound of formula (XV) Z is OH; the compound of formula (VII) is reacted with the compound of formula (XV) in the presence of a coupling agent such as HBTU, DCC, and the like.

The compound of formula (XVI) is de-protected by known methods, to yield the corresponding compound of formula (M1e).

Compounds of formula (M1) wherein X is $-C(O)-NR^1NR^2$ may be prepared according to the process outlined in Scheme 6.



Scheme 6

Accordingly, a suitably substituted compound of formula (V) is reacted with potassium cyanide, in a co-solvent such as methanol-water, and the like, preferably at room temperature, to yield the corresponding compound of formula (XVII).

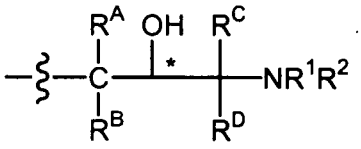
The compound of formula (XVII) is reacted with a base such as KOH, NaOH, and the like or with an acid such as H_2SO_4, HCl, and the like, or $NaBH_4$

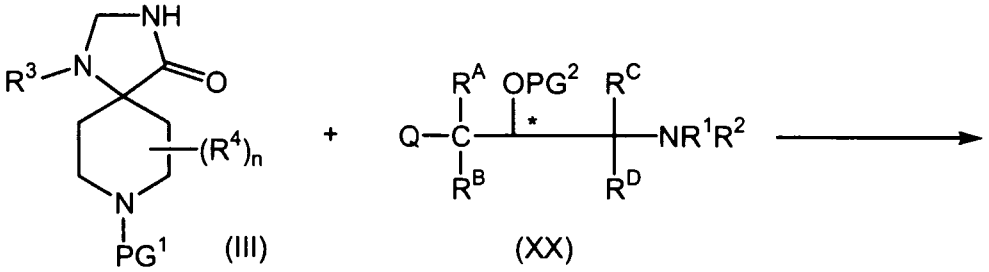
in the presence of $AlCl_3$, to yield the corresponding compound of formula (XVIII).

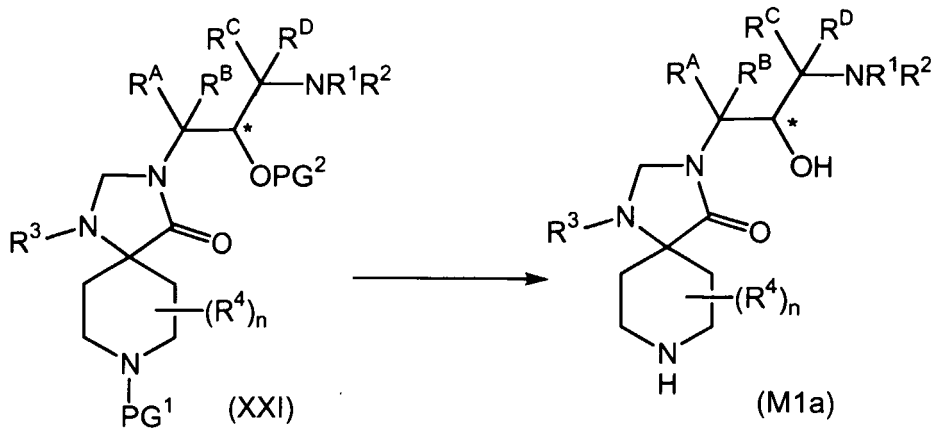
The compound of formula (XVIII) is reacted with a suitably substituted compound of formula (VI), a known compound or compound prepared by known methods, in the presence of a coupling agent such as DCC, EDCI, and the like, in an organic solvent such as CH_2Cl_2, THF, DMF, and the like, to yield the corresponding compound of formula (XIX).

The compound of formula (XIX) is de-protected by known methods, to yield the corresponding compound of formula (M1f).

Alternatively, the compound of formula (XVII) is reacted with a suitably substituted alcohol, a compound of the formula R^1-OH, a known compound or compound prepared by known methods, in the presence of an acid such as acetic acid, H_2SO_4, HCl, and the like, to yield the corresponding compound of formula (M1) wherein X is $C(O)NHR^1$. One skilled in the art will recognize that compounds of formula (M1) wherein X is $C(O)N(R^1)_2$ may be similarly prepared by reacting the compound of formula (XVII) with a suitably substituted alcohol of the formula R^1-OH, in the presence of an acid such as H_2SO_4, HCl, and the like, wherein the alcohol of formula R^1-OH is present in an excess amount.

Compounds of formula (M1a) wherein R^0 is  may alternatively be prepared according to the process outlined in Scheme 7.



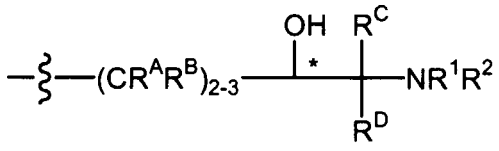


Scheme 7

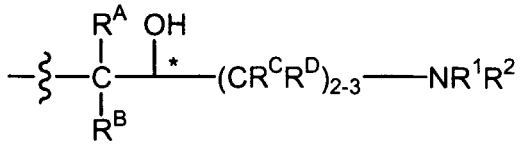
Accordingly, a suitably substituted compound of formula (III), is reacted with a suitably substituted compound of formula (XX), wherein Q is a suitable leaving group such as Cl, Br, I, tosylate, mesylate, and the like, and wherein PG^2 is a suitably protecting group such as benzyl, acyl, and the like, a known compound or compound prepared by known methods, in the presence of a base such as NaH, KO-t-Bu, K_2CO_3, NaHMDS, LiHMDS, and the like, in an organic solvent such as NMP, DMF, THF, and the like, to yield the corresponding compound of formula (XXI).

The compound of formula (XXI) is de-protected by known methods, to yield the corresponding compound of formula (M1a). One skilled in the art will recognize that the protecting groups PG^1 and PG^2 on the compound of formula (XXI) may be removed simultaneously or sequentially, in any order, by known methods.

One skilled in the art will recognize, that compounds of formula (M1) wherein R^0 is selected from the group consisting of

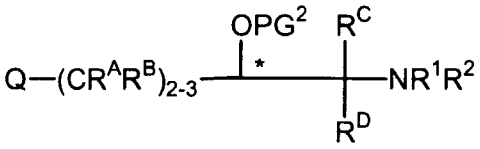


and



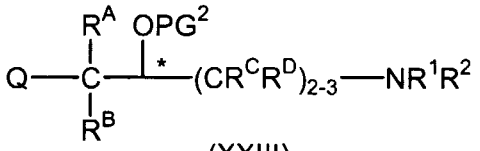
may be similarly prepared according to

the process outlined in Scheme 7 above, with selection and substitution of a suitably substituted compound of formula (XXII)



(XXII)

or the compound of formula (XXIII),

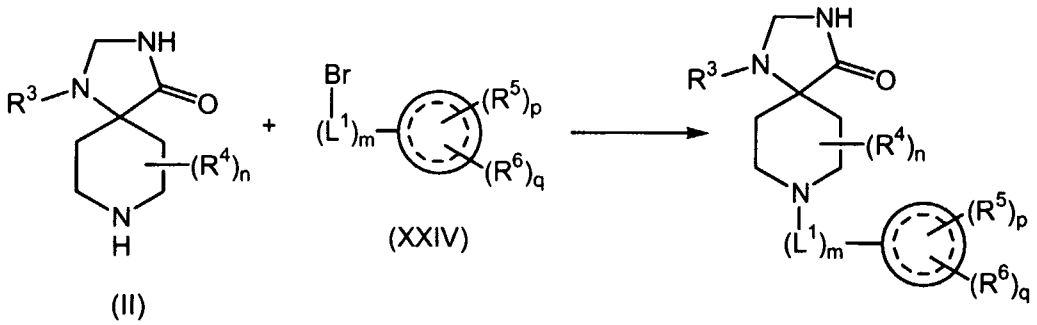


(XXIII)

respectively, for the compound of formula (XX).

One skilled in the art will recognize that the processes outlined in Schemes 2 to 7 above may be similarly applied to the preparation of compounds of formula (I) with substitution of a suitably substituted compound of formula (M2) for the compound of formula (II).

Compounds of formula (M2), wherein m is an integer from 0 to 1, provided that when  is aryl or heteroaryl, then m is 1, may be prepared according to the process outlined in Scheme 8.



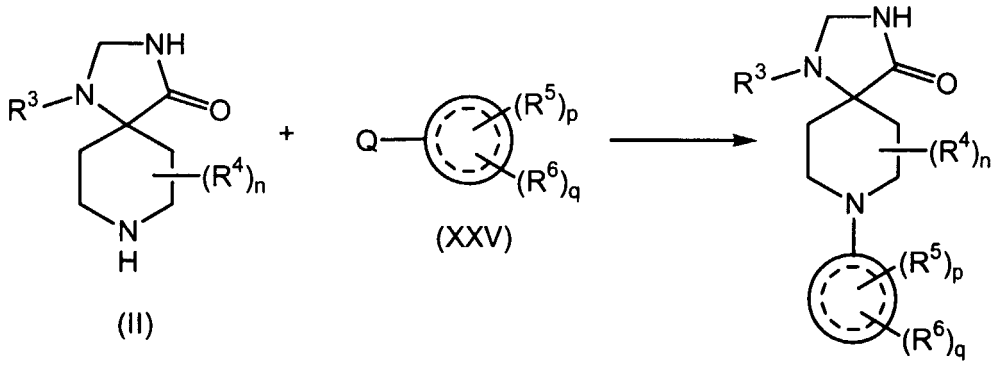
(II) (XXIV) (M2)

Scheme 8

Accordingly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted with a

suitably substituted compound of formula (XXIV), a known compound or compound prepared by known methods, in the presence of a base such as TEA, DIPEA, pyridine, Na_2CO_3, K_2CO_3, and the like, wherein the base is present in an amount equal to or greater than about one molar equivalent, in an organic solvent such as DMF, DMSO, NMP, and the like, to yield the corresponding compound of formula (M2).

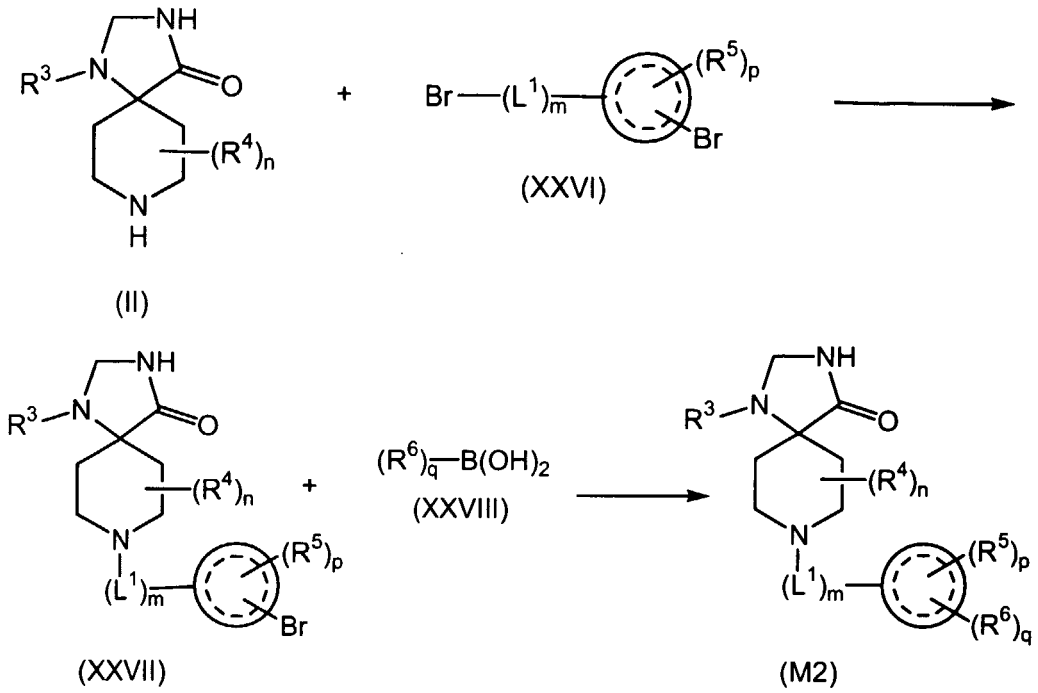
Compounds of formula (M2) wherein m is 0 and  is aryl or heteroaryl may be prepared according to the process outlined in Scheme 9.



Scheme 9

Accordingly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XXV), wherein Q is a suitable leaving group such as Cl, Br, I, triflate, and the like, a known compound or compound prepared by known methods, in the presence of a catalyst such as $Pd(OAc)_2$, $Pd_2(dba)_3$, and the like, in the presence of a phosphine ligand such as BINAP, $P(tBu)_3$, and the like, in the presence of a base such as Na_2CO_3, tBuONa, and the like, in an organic solvent such as toluene, dioxane, and the like, preferably at an elevated temperature in the range of about 30 to about 120°C, to yield the corresponding compound of formula (M2a).

Compounds of formula (M2) may alternatively be prepared according to the process outlined in Scheme 10.



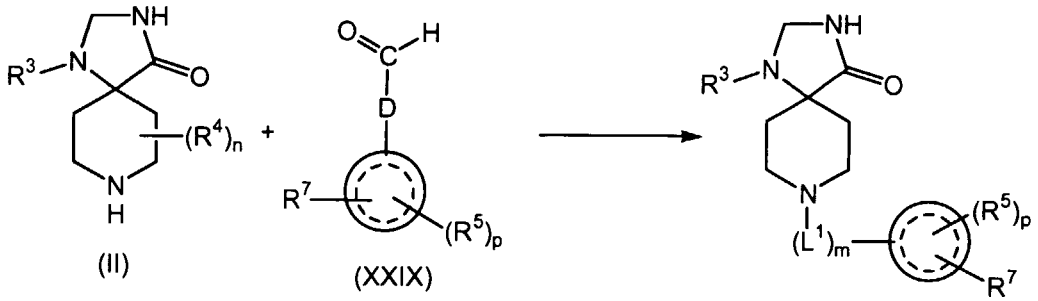
Scheme 10

Accordingly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XXVI), a known compound or compound prepared by known methods, in the presence of a base such as TEA, DIPEA, pyridine, Na_2CO_3, K_2CO_3, and the like, wherein the base is present in an amount equal to or greater than about one molar equivalent, in an organic solvent such as DMF, DMSO, NMP, and the like, to yield the corresponding compound of formula (XXVII).

The compound of formula (XXVII) is reacted with a suitably substituted boronic acid, a compound of formula (XXVIII), a known compound or compound prepared by known methods, in the presence of a catalyst such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and the like, in the presence of a base such as Na_2CO_3, K_3PO_4, and the like, in a non-protic organic solvent or mixture thereof, such as toluene, DME, DMF, and the like, or a mixture thereof such as toluene/ethanol, and the like, to yield the corresponding compound of formula (M2).

One skilled in the art will recognize that for compounds of formula (XXVI), the Br may alternatively be replaced with an I or triflate.

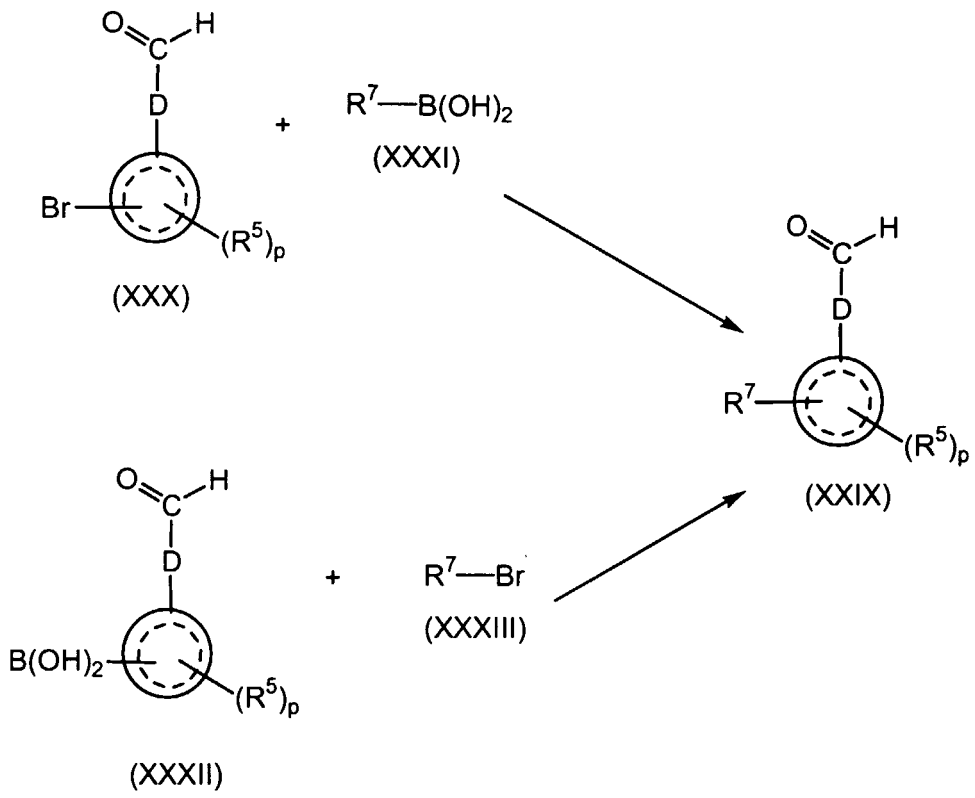
Compounds of formula (M2) wherein m is 1, L^1 is C_{1-6}alkyl or C_{3-6}alkenyl, R^6 is $(L^2)_0$-R^7 and R^7 is an aryl or heteroaryl group may be prepared according to the process outlined in Scheme 11.



Scheme 11

Accordingly, a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, is reacted with a suitably substituted aldehyde, a compound of formula (XXIX), wherein D is C_{1-5}alkyl or C_{2-5}alkenyl, a known compound or compound prepared by known methods, in the presence of a reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride, and the like, in the presence of an acid such as acetic acid, and the like, in an organic solvent such as DCE, THF, acetonitrile, and the like, to yield the corresponding compound of formula (M2a).

Compounds of formula (XXIX) may be prepared according to the processes outlined in Scheme 12.



Scheme 12

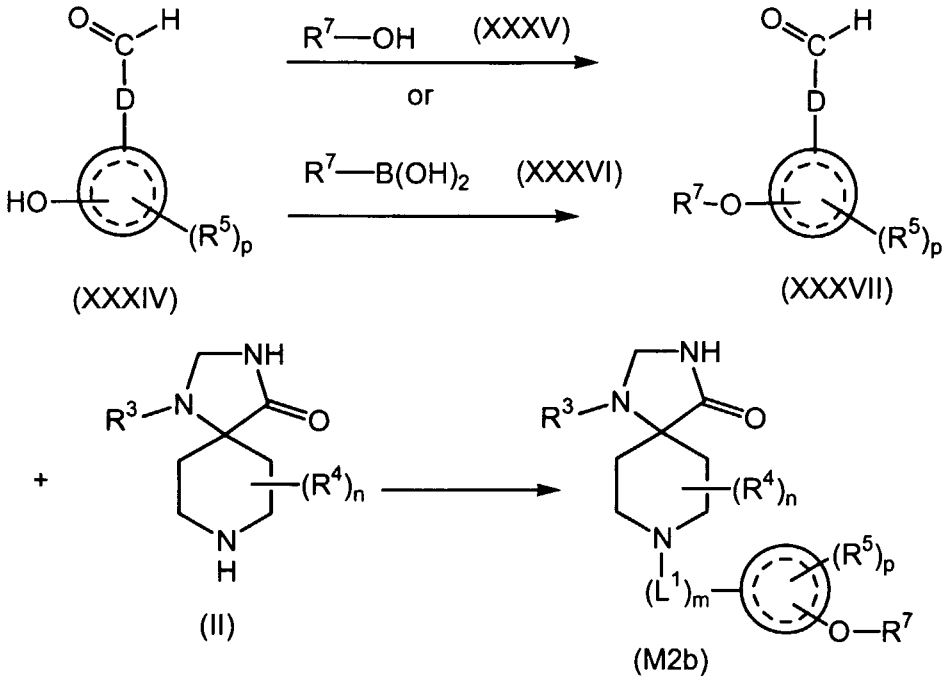
Accordingly, a suitably substituted compound of formula (XXX), wherein D is C_{1-5}alkyl or C_{2-5}alkenyl, a known compound or compound prepared by known methods, is reacted with a suitably substituted boronic acid, a compound of formula (XXXI), a known compound or compound prepared by known methods, in the presence of a catalyst such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and the like, in the presence of a base such as Na_2CO_3, $NaHCO_3$, K_3PO_4, and the like, in a non-protic organic solvent or mixture thereof such as toluene, toluene/ethanol, DME, DMF, benzene, and the like, to yield the corresponding compound of formula (XXIX).

Alternatively, a suitably substituted compound of formula (XXXII), wherein D is C_{1-5}alkyl or C_{2-5}alkenyl, a known compound or compound prepared by known methods, is reacted with a suitably substituted compound of formula (XXXIII), a known compound or compound prepared by known methods, in the presence of a catalyst such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and the like, in the presence of a base such as aqueous $NaHCO_3$, Na_2CO_3, K_3PO_4,

and the like, in an organic solvent such as DME, DMF, toluene, benzene, and the like, to yield the corresponding compound of formula (XXIX).

One skilled in the art will recognize that for compounds of formula (XXXI) and / or compounds of formula (XXXIII), the Br may alternatively be replaced with an I or triflate.

Compounds of formula (M2) wherein q is 1, R^6 is $(L^2)_1$-R^7 and L^2 is -O- may be prepared according to the process outlined in Scheme 13.



Scheme 13

Accordingly, a suitably substituted compound of formula (XXXIV), wherein D is C_{1-5}alkyl or C_{2-5}alkenyl, a known compound or compound prepared by known methods, is reacted with a suitably substituted alcohol, a compound of formula (XXXV), a known compound or compound prepared by known methods, in the presence of an activating agent such as tributylphosphine, triphenylphosphine, diphenyl-2-pyridylphosphine, and the like, in an anhydrous organic solvent such as benzene, THF, DCM, and the like, (via a Mitsunobu reaction) in the presence of a dehydrating agent such as 1,1'-(azodicarbonyl)dipiperidine, diethylazodicarboxylate,

diisopropylazodicarboxylate, and the like, to yield the corresponding compound of formula (XXXVII).

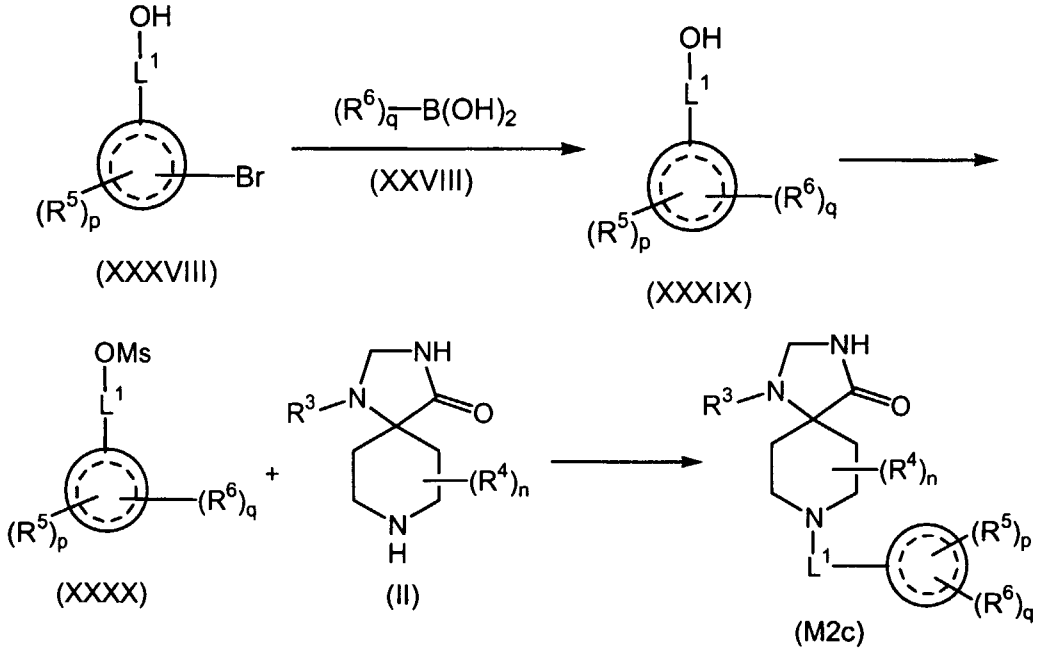
Alternatively, the compound of formula (XXXVII) may be prepared by reacting a compound of formula (XXXIV) with a compound of formula (XXXV), wherein the hydroxy (OH) group on the compound of formula (XXXV) is replaced with a fluoro, bromo or triflate, in the presence of a base such as K_2CO_3, sodium carbonate, sodium bicarbonate, and the like, in a dipolar aprotic solvent such as $(CH_3)_2NCOCH_3$, DMF, DMSO, and the like.

Alternatively, the compound of formula (XXXIV) is reacted with a suitably substituted boronic acid, a compound of formula (XXXVI), a known compound or compound prepared by known methods, in the presence of a catalyst such as copper (II) acetate, and the like, in the presence of an base such as TEA, pyridine, and the like, in the presence of molecular sieves, preferably 4 Angstrom molecular sieves, in an organic solvent such as DCM, DCE, and the like, preferably at ambient temperature, to yield the corresponding compound of formula (XXXVII).

The compound of formula (XXXVII) is reacted with a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, in the presence of a reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride, and the like, in an organic solvent such as DCE, THF, acetonitrile, and the like, to yield the corresponding compound of formula (M2b).

One skilled in the art will recognize that compounds of formula (M2) wherein L^2 is -S- may similarly be prepared according to the process outlined above with appropriate selection and substitution of suitably substituted starting materials (e.g. substitution of the OH group on the compound of formula (XXXIV) with Cl or Br and substitution of a suitably substituted compound of the formula R^7-SH for the compound of formula (XXXV), preferably in the presence of a copper catalyst, according to known methods. The sulfur group may then be further oxidized with a suitable oxidizing agent such as hydrogen peroxide, mCPBA, and the like, according to known methods, to yield the corresponding compound wherein L^2 is selected from -SO- or -SO_2-.

Compounds of formula (M2) wherein R^6 is $-L^2-R^7$ and L^2 is C_{2-4}alkenyl may be prepared according to the process outlined in Scheme 14.



Scheme 14

Accordingly, a suitably substituted compound of formula (XXXVIII), a known compound or compound prepared by known methods, is reacted with a suitably substituted boronic acid, a compound of formula (XXVIII), a known compound or compound prepared by known methods, in the presence of a catalyst such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and the like, in the presence of a base such as $NaHCO_3$, K_2CO_3, Na_2CO_3, and the like, to yield the corresponding compound of formula (XXXIX).

The compound of formula (XXXIX) is reacted with methanesulfonyl chloride, a known compound, in the presence of an organic base such as TEA, DIPEA, N-methylmorpholine, and the like, in an aprotic solvent such as DCM, THF, acetonitrile, $CHCl_3$, and the like, to yield the corresponding compound of formula (XXXX), wherein Ms is a mesyl group.

The compound of formula (XXXX) is reacted with a suitably substituted compound of formula (II), a known compound or compound prepared by known methods, in the presence of a reducing agent such as sodium triacetoxyborohydride, sodium cyanoborohydride, and the like, in an organic

solvent such as DCM, DCE, THF, methanol, acetonitrile, and the like, to yield the corresponding compound of formula (M2c).

One skilled in the art will recognize that the processes outlined in Schemes 8 to 14 above may be similarly applied to the preparation of compounds of formula (I) with substitution of a suitably substituted compound of formula (M1) for the compound of formula (II).

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.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds which are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound *in vivo* after administration to the 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.

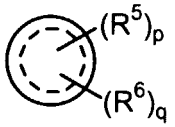
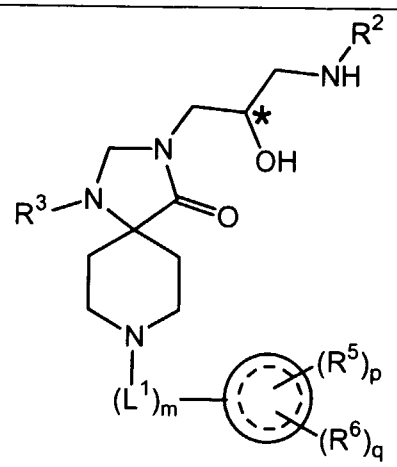
Following the procedures described herein, representative compounds of the present invention were prepared as listed in Tables 1-8. In the Tables below, the column headed with a * shall define the stereochemical configuration of the bond denoted with the "*" symbol in the general structure at the head of the table. In addition to "R" and "S" designations, racemic mixtures will be denoted with the term "Rac". For the  substituent, the stereoconfiguration is racemic, unless otherwise noted with an "R" or "S". In the columns headed $(L^1)_m$, a listing of "absent" shall mean that m is 0.

Table 1



ID#	*	R^2	R^3	$(L^1)_m$	$(R^5)_p$ $(R^6)_q$
1	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH_2	cyclooctyl
2	R	3,4-dimethoxy benzyl	4-fluorophenyl	CH_2	cyclooctyl
3	R	3,5-di(trifluoro methyl)benzyl	4-fluorophenyl	CH_2	cyclooctyl
4	R	2-(4-imidazolyl) ethyl	4-fluorophenyl	CH_2	cyclooctyl
5	R	4-bromobenzyl	4-fluorophenyl	CH_2	cyclooctyl
6	R	3,4-dimethoxy benzyl	4-fluorophenyl	CH_2	cyclooctyl
7	S	2,4-difluorobenzyl	4-fluorophenyl	CH_2	cyclooctyl
8	S	2,4-dimethoxy benzyl	4-fluorophenyl	CH_2	cyclooctyl
9	S	4-biphenyl	4-fluorophenyl	CH_2	cyclooctyl
10	S	2-ethoxybenzyl	4-fluorophenyl	CH_2	cyclooctyl
11	S	2-phenylethyl	4-fluorophenyl	CH_2	cyclooctyl
12	S	2,5-difluorobenzyl	4-fluorophenyl	CH_2	cyclooctyl
13	S	2-(5-bromopyridyl)	4-fluorophenyl	CH_2	cyclooctyl
14	S	2-methoxybenzyl	4-fluorophenyl	CH_2	cyclooctyl
15	S	4-bromobenzyl	4-fluorophenyl	CH_2	cyclooctyl

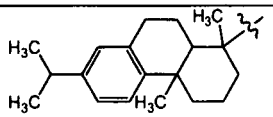
16	S	3,5-di(trifluoro methyl)benzyl	4-fluorophenyl	CH_2	cyclooctyl
17	S	1-adamantanyl-methyl	4-fluorophenyl	CH_2	cyclooctyl
18	S	3-methylbenzyl	4-fluorophenyl	CH_2	cyclooctyl
19	S	2-(2,5-dimethoxy-2,5-dihydro-furyl)-methyl	4-fluorophenyl	CH_2	cyclooctyl
20	S	3-bromobenzyl	4-fluorophenyl	CH_2	cyclooctyl
21	S	3-chlorobenzyl	4-fluorophenyl	CH_2	cyclooctyl
22	S	3,4-dimethoxy benzyl	4-fluorophenyl	CH_2	cyclooctyl
23	S	4-nitrobenzyl	4-fluorophenyl	CH_2	cyclooctyl
24	S	4-pyridyl	4-fluorophenyl	CH_2	cyclooctyl
25	S	3,5-dimethoxy-benzyl	4-fluorophenyl	CH_2	cyclooctyl
26	S	2-(2-thienyl)ethyl	4-fluorophenyl	CH_2	cyclooctyl
27	S	2-methylbenzyl	4-fluorophenyl	CH_2	cyclooctyl
28	S	2-(4-imidazolyl)-ethyl	4-fluorophenyl	CH_2	cyclooctyl
29	S	4-trifluoromethyl benzyl	4-fluorophenyl	CH_2	cyclooctyl
30	S	2-(4-bromophenyl) ethyl	4-fluorophenyl	CH_2	cyclooctyl
31	S	2,4-dichlorobenzyl	4-fluorophenyl	CH_2	cyclooctyl
32	S	3-pyridylmethyl	4-fluorophenyl	CH_2	cyclooctyl
33	S	3-trifluoromethyl benzyl	4-fluorophenyl	CH_2	cyclooctyl
34	S	2-(4-methoxy-phenyl)ethyl	4-fluorophenyl	CH_2	cyclooctyl
35	S	3-methoxybenzyl	4-fluorophenyl	CH_2	cyclooctyl
36	S	4-pyridyl	4-fluorophenyl	CH_2	cyclooctyl
38	S	2-(3,4-dimethoxy phenyl)ethyl	4-fluorophenyl	CH_2	cyclooctyl
39	S	2-pyridylmethyl	4-fluorophenyl	CH_2	cyclooctyl

40	S	1-naphthyl	4-fluorophenyl	CH_2	cyclooctyl
41	S	4-methylbenzyl	4-fluorophenyl	CH_2	cyclooctyl
42	S	2-(3,5-dimethyl-pyridyl)	4-fluorophenyl	CH_2	cyclooctyl
43	S	3,4,5-trimethoxy-benzyl	4-fluorophenyl	CH_2	cyclooctyl
44	S	2-bromobenzyl	4-fluorophenyl	CH_2	cyclooctyl
45	S	2,3-dimethoxy benzyl	4-fluorophenyl	CH_2	cyclooctyl
46	S	3,4-dichlorobenzyl	4-fluorophenyl	CH_2	cyclooctyl
47	R	2-(4-morpholinyl) ethyl	4-fluorophenyl	absent	1-acenaphthenyl
48	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
49	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
50	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH_2CH_2	phenyl
51	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH_2CH_2	phenyl
52	Rac	2-(3,4-dimethoxy-phenyl)ethyl	phenyl	absent	1-acenaphthenyl
53	R	2-(4-morpholinyl) ethyl	phenyl	absent	1-acenaphthenyl
251	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH_2	1-naphthyl
253	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH_2	1-naphthyl
254	S	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	CH_2	1-naphthyl

255	S	2-(2-nitro-4,5-dimethoxy-phenyl) ethyl	4-fluorophenyl	CH_2	1-naphthyl
259	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH_2	2-naphthyl
261	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH_2	2-naphthyl
262	S	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	CH_2	2-naphthyl
265	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH_2	4-chlorophenyl
267	R	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH_2	4-chlorophenyl
268	R	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	CH_2	4-chlorophenyl
269	R	2-(2-nitro-4,5-dimethoxy-phenyl) ethyl	4-fluorophenyl	CH_2	4-chlorophenyl
271	R	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
276	S	2-(2-nitro-4,5-dimethoxy-phenyl) ethyl	4-fluorophenyl	absent	1-acenaphthenyl
279	S	1-(t-butoxy-carbonyl)-2-phenylethyl	4-fluorophenyl	CH_2	cyclooctyl
281	S	2-ethoxy-phenyl	4-fluorophenyl	CH_2	cyclooctyl
282	S	4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl) phenyl	4-fluorophenyl	CH_2	cyclooctyl
285	S	4-cyclohexyl-phenyl	4-fluorophenyl	CH_2	cyclooctyl

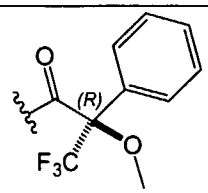
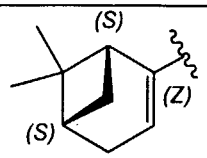
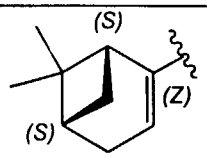
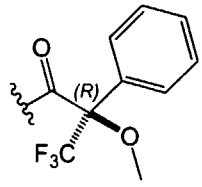
292	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH_2	5-phenyl-2-thienyl
293	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH_2	5-phenyl-2-thienyl
298	R	2-(4-morpholinyl) ethyl	4-fluorophenyl	absent	1-acenaphthenyl
300	R	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
307	S	3,4-dimethoxy-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
308	S	4-nitrobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
309	S	2-(1,2,3,4-tetrahydro-isoquinolinyl)	4-fluorophenyl	absent	1-acenaphthenyl
310	S	4-biphenyl	4-fluorophenyl	absent	1-acenaphthenyl
311	S	2-furylmethyl	4-fluorophenyl	absent	1-acenaphthenyl
312	S	3-iodobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
314	S	3,4-difluorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
315	S	3-bromobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
316	S	4-chlorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
317	S	4-methoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
318	S	2-methoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
319	S	3,5-di(trifluoromethyl) benzyl	4-fluorophenyl	absent	1-acenaphthenyl
320	S	3,4,5-trimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
321	S	3-fluorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
322	S	3-methoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
323	S	2-(4-methoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
324	S	3,5-dimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl

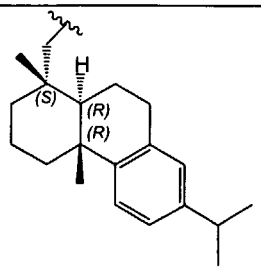
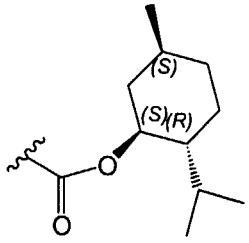
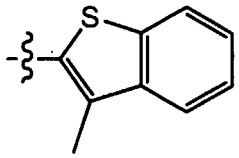
325	S	4-methyl-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
326	S	3-(phenyl)-n-propyl	4-fluorophenyl	absent	1-acenaphthenyl
327	S	4-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
328	S	4-trifluoromethoxy benzyl	4-fluorophenyl	absent	1-acenaphthenyl
329	S	2-(phenoxy)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
330	S	2-methyl-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
331	S	2,3-dimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
338	S	3-di(n-butyl)amino-n-propyl	4-fluorophenyl	absent	1-acenaphthenyl
341	S	2-phenylethyl	4-fluorophenyl	absent	1-acenaphthenyl
342	S	2,5-difluoro-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
343	S	3,4-dichloro-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
344	S	3-trifluoromethyl benzyl	4-fluorophenyl	absent	1-acenaphthenyl
345	S	benzyl	4-fluorophenyl	absent	1-acenaphthenyl
346	S	2-fluoro-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
347	S	4-trifluoromethyl benzyl	4-fluorophenyl	absent	1-acenaphthenyl
348	S	4-methoxycarbonyl-benzyl	4-fluorophenyl	absent	1-acenaphthenyl
349	S	2,4-dimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
350	S	3-chlorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
351	S	3-ethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
352	S	4-bromobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
353	S	3-methylbenzyl	4-fluorophenyl	absent	1-acenaphthenyl
354	S	4-fluorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
355	S	2-bromobenzyl	4-fluorophenyl	absent	1-acenaphthenyl

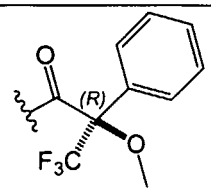
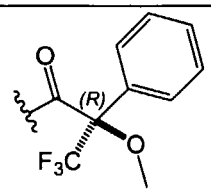
356	S	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
358	S	2,4-difluorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
365	S	2-(4-bromophenyl) ethyl	4-fluorophenyl	absent	1-acenaphthenyl
366	S	3-pyridyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl
367	S	2,4,6-trimethoxybenzyl	4-fluorophenyl	absent	1-acenaphthenyl
368	S	2,4-dichlorobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
370	S	3-nitrobenzyl	4-fluorophenyl	absent	1-acenaphthenyl
371	S	1-naphthyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl
372	S	2-(2-thienyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
373	S	2-trifluoromethyl benzyl	4-fluorophenyl	absent	1-acenaphthenyl
385	R	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH_2	1-(8-methyl-naphtyl)
386	S	2-(3,4-dimethoxy-phenyl)ethyl	4-fluorophenyl	CH_2	1-(8-methyl-naphtyl)
387	R	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH_2	1-(8-methyl-naphtyl)
374	S		4-fluorophenyl	absent	1-acenaphthenyl
375	S	2-(4,6-dimethyl)-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
376	S	4-pyridyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl
378	R	2-pyridyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl
379	R	4-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
380	R	3-(6-methoxy-pyridyl)	4-fluorophenyl	absent	1-acenaphthenyl
381	R	3-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl

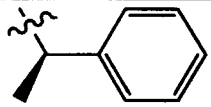
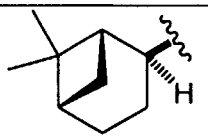
383	R	2-(5-methyl-pyridyl)	4-fluorophenyl	absent	1-acenaphthenyl
390	R	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
392	R	4-methoxybenzyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
393	R	4-pyridyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
396	S	2-(4-morpholinyl) ethyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
398	S	4-methoxybenzyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
418	S	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
419	S	2-pyridyl	4-fluorophenyl	absent	1-acenaphthenyl
420	R	H	4-fluorophenyl	absent	R-1-acenaphthenyl
421	R	2-pyridyl	4-fluorophenyl	absent	R-1-acenaphthenyl
422	S	H	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
424	S	H	4-fluorophenyl	absent	R-1-acenaphthenyl
425	R	methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
426	R	H	4-fluorophenyl	absent	S-1-acenaphthenyl
427	R	methyl	4-fluorophenyl	absent	S-1-acenaphthenyl
430	S	H	4-fluorophenyl	absent	S-1-acenaphthenyl
431	S	methyl	4-fluorophenyl	absent	S-1-acenaphthenyl
437	S	methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
438	R	H	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
443	S	methoxy	4-fluorophenyl	absent	R-1-acenaphthenyl
444	S	ethoxy	4-fluorophenyl	absent	R-1-acenaphthenyl
446	R	2-(3,4-methylene dioxyphenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
448	S	2-phenoxyethyl	4-fluorophenyl	absent	1-acenaphthenyl

451	S	4-(1-phenyl-2-pyrazolyl-amino-sulfonyl)phenyl	4-fluorophenyl	CH_2	cyclooctyl
452	S	4-carboxy-benzyl	4-fluorophenyl	CH_2	cyclooctyl
453	S	H	4-fluorophenyl	CH_2	cyclooctyl
454	S	n-butyl	4-fluorophenyl	CH_2	cyclooctyl
458	S	phenyl	4-fluorophenyl	CH_2	2-trifluoromethyl-6-chloro-phenyl
461	R	2-(2-nitro-4,5-dimethoxy-phenyl)ethyl	4-fluorophenyl	absent	1-acenaphthenyl
463	S	benzyloxy	4-fluorophenyl	absent	R-1-acenaphthenyl
464	R	4-(aminoethyl)-phenyl	4-fluorophenyl	absent	S-1-acenaphthenyl
600	S	phenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
601	R	4-(t-butoxycarbonyl-amino-ethyl)-phenyl	4-fluorophenyl	absent	S-1-acenaphthenyl
602	S	4-fluorophenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
603	S	3,4-(dimethoxy)-phenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
604	S	4-(methyl)-phenyl	4-fluorophenyl	absent	R-1-acenaphthenyl
605	R	2-(aminoethyl)-phenyl	4-fluorophenyl	absent	S-1-acenaphthenyl
606	S	1-cyclopropyl	4-fluorophenyl	absent	R-1-acenaphthenyl
607	S	1-Adamantanyl	4-fluorophenyl	CH_2	3,5-bis-trifluoromethyl-phenyl
608	S	4-pyridyl	4-fluorophenyl	CH_2	3,5-bis-trifluoromethyl-phenyl
609	S	1-(3-pyridyl)-methyl	4-fluorophenyl	CH_2	3,5-bis-trifluoromethyl-phenyl
610	S	3-di(n-butyl)amino-n-propyl	4-fluorophenyl	CH_2	3,5-bis-trifluoromethyl-phenyl

611	R	1-(3-pyridyl)-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
612	S	1-(4-pyridyl)-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
613	S	1-(3-pyridyl)-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
614	S	1-(2-thienyl)-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
615	R		4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
616	S	H	4-fluorophenyl	absent	cyclooctyl
617	S	4-pyridinyl	4-fluorophenyl	absent	cyclooctyl
618	S	4-pyridinyl	4-fluorophenyl	CH_2	
619	S	H	4-fluorophenyl	CH_2	
620	R	H	4-fluorophenyl	CH_2	cyclooctyl
621	R	4-pyridinyl	4-fluorophenyl	CH_2	cyclooctyl
622	S		4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
623	R	H	4-fluorophenyl	absent	cyclooctyl
624	R	n-butyl	4-fluorophenyl	absent	cyclooctyl
625	R	3-nitrobenzyl	4-fluorophenyl	absent	cyclooctyl

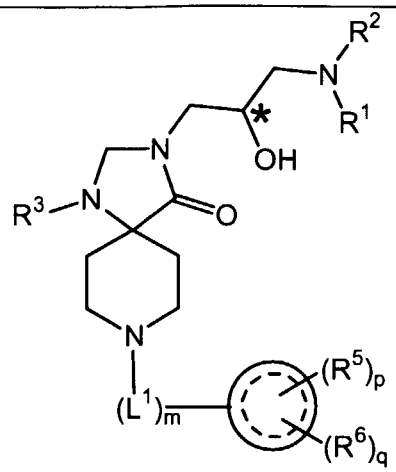
626	R		4-fluorophenyl	absent	cyclooctyl
627	R	4-pyridinyl	4-fluorophenyl	absent	cyclooctyl
628	R	4-methoxycarbonyl-benzyl	4-fluorophenyl	absent	cyclooctyl
629	R	1-[2-(3H-imidazol-4-yl)-ethyl]	4-fluorophenyl	absent	cyclooctyl
630	-		4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
631	R	C(O)O-t-butyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
632	R	H	4-fluorophenyl	$CH(CH_3)$	
633	S	dimethylamino-n-propyl	4-fluorophenyl	CH_2	cyclooctyl
634	S	3-hydroxy-n-propyl	4-fluorophenyl	CH_2	cyclooctyl
635	R	3-hydroxy-n-propyl	4-fluorophenyl	CH_2	cyclooctyl
636	R	dimethylamino-n-propyl	4-fluorophenyl	CH_2	cyclooctyl
637	S	3-hydroxy-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
638	S	dimethylamino-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl

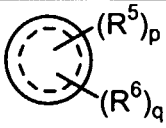
639	R	3-hydroxy-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
640	R	H	phenyl	absent	1S-(3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl
641	S	3-methoxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
642	S	3-hydroxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
643	R	3-hydroxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
644	R	3-methoxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
645	R		4-fluorophenyl	absent	R-1-acenaphthenyl
646	S		4-fluorophenyl	absent	R-1-acenaphthenyl
647	R	dimethylamino-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
648	S	methyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
649	S	3-hydroxy-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
650	S	3-methoxy-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
651	R	3-hydroxy-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
652	R	3-methoxy-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
653	S	dimethylamino-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)

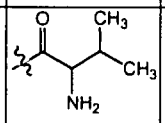
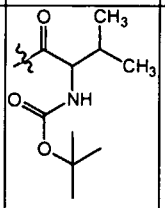
654	S	methylamino-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
655	S	methylamino-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
656	R	methylamino-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
657	R	methylamino-n-propyl	4-fluorophenyl	CH_2	cyclooctyl
658	S	methylamino-n-propyl	phenyl	absent	1S-(3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl
659	S	H	phenyl	absent	1S-(3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl
660	R	methyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
661	R	methylamino-ethyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
662	R	1-(4-ethoxycarbonyl-piperidinyl)	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
663	R		4-fluorophenyl	absent	S-1-acenaphthenyl
664	R	methylamino-n-propyl	4-fluorophenyl	CH_2	
665	R	t-butoxycarbonyl-amino-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
666	R	dimethylamino-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)

667	R	N-methyl-N-t-butoxycarbonyl-amino-ethyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)

Table 2



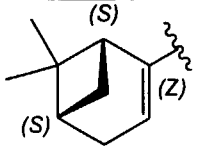
ID#	*	R^1	R^2	R^3	$(L^1)_m$	
54	S	n-butyl	benzyl	phenyl	absent	(3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-2-yl
55	S	ethyl	4-methyl benzyl	4-fluoro-phenyl	absent	1-acenaphthenyl
56	S	t-butyl	benzyl	4-fluoro-phenyl	absent	1-acenaphthenyl
57	S	ethyl	4-methyl benzyl	4-fluoro-phenyl	absent	4-n-propyl-cyclohexyl
58	S	ethyl	4-methyl benzyl	4-fluoro-phenyl	CH_2CH_2	phenyl
59	S	t-butyl	benzyl	4-fluoro-phenyl	absent	4-n-propyl-cyclohexyl
60	S	t-butyl	benzyl	4-fluoro-phenyl	CH_2CH_2	phenyl

61	Rac	ethyl	4-methyl benzyl	phenyl	absent	1-acenaphthenyl
62	Rac	t-butyl	benzyl	phenyl	absent	1-acenaphthenyl
63	S	2-(dimethyl amino)ethyl	benzyl	4-fluoro-phenyl	CH_2	cyclooctyl
64	S	n-butyl	benzyl	4-fluoro-phenyl	CH_2	cyclooctyl
65	S	benzyl	2-phenyl-ethyl	4-fluoro-phenyl	CH_2	cyclooctyl
78	S		4-methyl benzyl	4-fluoro phenyl	CH_2	cyclooctyl
79	S		4-methyl benzyl	4-fluoro phenyl	CH_2	cyclooctyl
250	S	t-butyl	benzyl	4-fluoro phenyl	CH_2	1-naphthyl
252	S	ethyl	4-methyl benzyl	4-fluoro-phenyl	CH_2	1-naphthyl
256	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	CH_2	1-naphthyl
258	S	ethyl	4-methyl benzyl	4-fluoro-phenyl	CH_2	2-naphthyl
260	S	t-butyl	benzyl	4-fluoro-phenyl	CH_2	2-naphthyl
263	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	CH_2	2-naphthyl

264	S	ethyl	4-methyl benzyl	4-fluoro-phenyl	CH_2	4-chlorophenyl
266	S	t-butyl	benzyl	4-fluoro-phenyl	CH_2	4-chlorophenyl
270	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	CH_2	4-chlorophenyl
275	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	absent	1-acenaphthenyl
280	S	n-butyl	benzyl	4-fluoro-phenyl	CH_2	2,3,4,5,6-pentamethyl-phenyl
283	S	methyl	3-(2-pyridyl)-n-propyl	4-fluoro-phenyl	CH_2	cyclooctyl
289	S	benzyl	(1S,2S)-1-hydroxy-cyclopent-2-yl-methyl	4-fluoro-phenyl	CH_2	cyclooctyl
290	S	benzyl	(1S,2S)-1-hydroxy-cyclohex-2-yl-methyl	4-fluoro-phenyl	CH_2	cyclooctyl
291	S	benzyl	(1S,2S)-1-hydroxy-cyclohept-2-yl-methyl	4-fluoro-phenyl	CH_2	cyclooctyl
294	S	ethyl	4-methyl benzyl	4-fluoro-phenyl	CH_2	5-phenyl-2-thienyl
295	Rac	methyl	2-(3,4-dimethoxy-phenyl)ethyl	phenyl	absent	1-acenaphthenyl

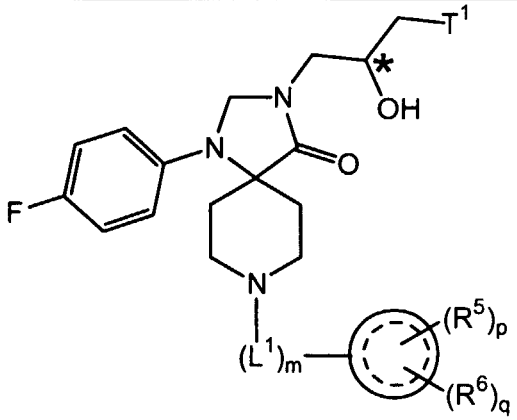
299	R	t-butyl	benzyl	4-fluoro-phenyl	absent	1-acenaphthenyl
305	R	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	absent	1-acenaphthenyl
313	S	benzyl	2-phenylethyl	4-fluoro-phenyl	absent	1-acenaphthenyl
339	R	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	absent	R-1-acenaphthenyl
340	R	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	absent	S-1-acenaphthenyl
362	S	benzyl	benzyl	4-fluoro-phenyl	absent	1-acenaphthenyl
364	S	methyl	2-(2-pyridyl) ethyl	4-fluoro-phenyl	absent	1-acenaphthenyl
389	R	t-butyl	benzyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
391	R	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
394	S	ethyl	4-methyl benzyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
395	S	t-butyl	benzyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
399	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
423	R	methyl	methyl	4-fluoro-phenyl	absent	R-1-acenaphthenyl

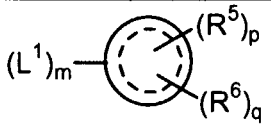
428	R	methyl	methyl	4-fluoro-phenyl	absent	S-1-acenaphthenyl
429	R	methyl	ethyl	4-fluoro-phenyl	absent	S-1-acenaphthenyl
432	S	methyl	methyl	4-fluoro-phenyl	absent	S-1-acenaphthenyl
433	S	methyl	ethyl	4-fluoro-phenyl	absent	S-1-acenaphthenyl
434	R	methyl	ethyl	4-fluoro-phenyl	absent	R-1-acenaphthenyl
435	S	methyl	methyl	4-fluoro-phenyl	absent	R-1-acenaphthenyl
436	S	methyl	ethyl	4-fluoro-phenyl	absent	R-1-acenaphthenyl
439	S	methyl	methyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
440	S	methyl	ethyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
441	R	methyl	methyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
442	R	methyl	ethyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
455	S	4-methyl-benzyl	6-methylthio-2-pyridyl-carbonyl	4-fluoro-phenyl	CH_2	cyclooctyl
456	S	n-butyl	benzyl	4-fluoro-phenyl	CH_2	2-trifluoromethyl-6-chloro-phenyl
457	S	methyl	2-(3,4-dimethoxy-phenyl)ethyl	4-fluoro-phenyl	CH_2	2-trifluoromethyl-6-chloro-phenyl

459	S	benzyl	2-(dimethyl-amino)ethyl	4-fluoro-phenyl	CH_2	2-trifluoromethyl-6-chloro-phenyl
462	R	ethyl	4-methyl-benzyl	4-fluoro-phenyl	absent	1-acenaphthenyl
668	S	ethyl	phenyl	4-fluoro-phenyl	absent	R-1-acenaphthenyl
669	S	methyl	phenyl	4-fluoro-phenyl	absent	R-1-acenaphthenyl
670	S	ethoxy-carbonyl-methyl	benzyl	4-fluoro-phenyl	CH_2	3,5-bis-trifluoromethyl-phenyl
671	S	n-butyl	benzyl	4-fluoro-phenyl	CH_2	3,5-bis-trifluoromethyl-phenyl
672	S	1-phenyl-ethyl	benzyl	4-fluoro-phenyl	CH_2	3,5-bis-trifluoromethyl-phenyl
673	S	2-(3,4-dimethoxy-phenyl)-ethyl	methyl	4-fluoro-phenyl	CH_2	3,5-bis-trifluoromethyl-phenyl
674	S	(dimethyl-amino)-ethyl	benzyl	4-fluoro-phenyl	CH_2	3,5-bis-trifluoromethyl-phenyl
675	S	2-(3,4-dimethoxy-phenyl)-ethyl	methyl	4-fluoro-phenyl	absent	cyclooctyl
676	S	benzyl	n-butyl	4-fluoro-phenyl	absent	cyclooctyl
677	S	benzyl	n-butyl	4-fluoro-phenyl	CH_2	

678	R	2-(3,4-dimethoxy-phenyl)-ethyl	methyl	4-fluoro-phenyl	CH_2	cyclooctyl
679	S	t-butoxy-carbonyl	methyl	4-fluoro-phenyl	absent	R-1-acenaphthenyl
680	S	t-butoxy-carbonyl	methyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)
681	R	amino-n-propyl	methyl	4-fluoro-phenyl	CH_2	1-(8-methyl-naphthyl)

Table 3



ID#	*	T^1 (NR^1R^2 taken together)	
66	S	1-(4-(3-trifluoromethyl-phenyl)-piperazinyl)	cyclooctyl-methyl
67	S	1-(4-piperidinyl-piperidinyl)	cyclooctyl-methyl
68	S	1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl)	cyclooctyl-methyl
69	S	1-(3-(diethylaminocarbonyl)-piperidinyl)	cyclooctyl-methyl
70	S	1-(2,3-dihydro-1H-pyrrolyl)	cyclooctyl-methyl
71	S	1-(4-[(4-chlorophenyl)-phenylmethyl]-piperazinyl)	cyclooctyl-methyl

72	S	2-(1,2,3,4-tetrahydro-isoquinolinyl)	cyclooctyl-methyl
73	S	1-(4-t-butoxycarbonyl-piperazinyl)	cyclooctyl-methyl
74	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	cyclooctyl-methyl
75	S	4-(2,6-dimethyl-morpholinyl)	cyclooctyl-methyl
76	S	1-(4-benzyl-piperazinyl)	cyclooctyl-methyl
115	S	2-(1,2,3,4-tetrahydro-isoquinolinyl)	2-(2-(2-thienyl)-phenyl)ethyl
160	R	1-(4-t-butoxycarbonyl-piperazinyl)	2-(2-(2-thienyl)-phenyl)ethyl
165	S	1-(4-t-butoxycarbonyl-piperazinyl)	2-(2-(2-thienyl)-phenyl)-ethyl
166	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	2-(2-(2-thienyl)-phenyl)ethyl
181	R	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	2-(2-(2-thienyl)-phenyl)ethyl
183	R	1-pyrrolidinyl	2-(2-(2-thienyl)-phenyl)ethyl
188	R	1-(4-ethoxycarbonyl-piperidinyl)	2-(2-(2-thienyl)-phenyl)-ethyl
257	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	2-(2-(2-thienyl)-phenyl)ethyl
284	S	1-(2S-(phenylamino-methyl)-pyrrolidinyl)	cyclooctyl-methyl
682	S	2-(1,2,3,4-tetrahydro-isoquinolinyl)	3,5-bis-trifluoromethyl-benzyl
683	S	1-[4-(3-trifluoromethyl-phenyl)-piperazinyl]	3,5-bis-trifluoromethyl-benzyl
684	S	1-(4-ethoxycarbonyl-piperidinyl)	3,5-bis-trifluoromethyl-benzyl
685	S	1-(2,3-dihydro-pyrrolidinyl)	3,5-bis-trifluoromethyl-benzyl

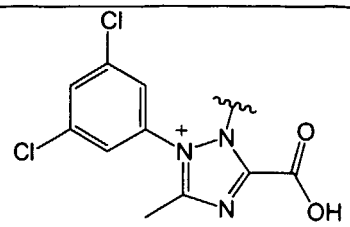
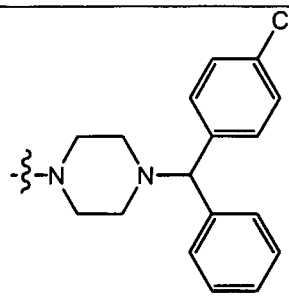
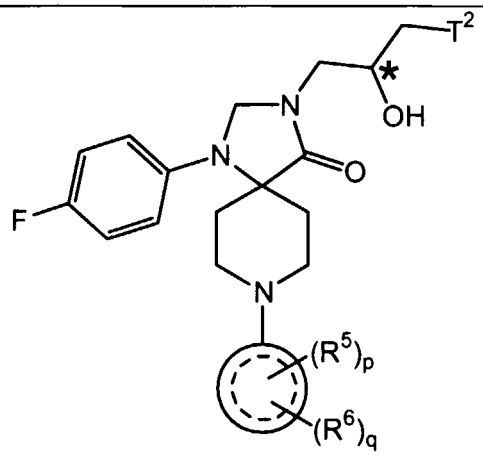
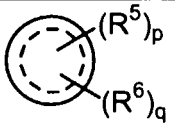
686	S	3-(diethylaminocarbonyl)-piperidinyl	3,5-bis-trifluoromethyl-benzyl
687	S		cyclooctyl
688	R	1-(3,4-dihydroxy-2,5-bis-hydroxymethyl-pyrrolidinyl)	cyclooctyl
689	R	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	cyclooctyl
690	R		cyclooctyl

Table 4

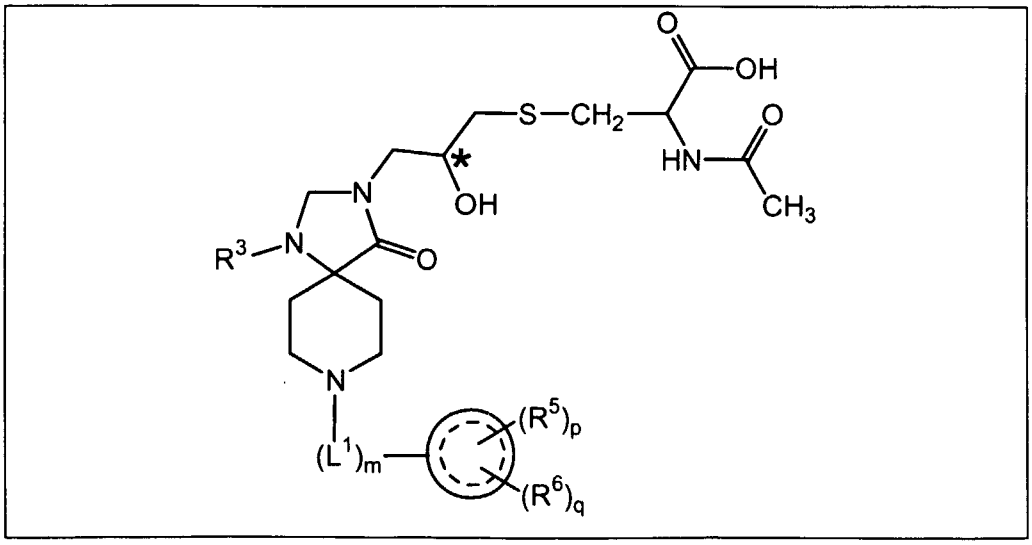


ID#	*	T^2 (NR^1R^2 taken together)	
296	R	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	1-acenaphthenyl

332	S	1-(4-benzyl-piperazinyl)	1-acenaphthenyl
333	S	1-(4-(3-trifluoromethyl-phenyl)-piperazinyl)	1-acenaphthenyl
334	S	1-(4-(1-piperidinyl)-piperidinyl)	1-acenaphthenyl
335	S	1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl)	1-acenaphthenyl
336	S	1-(3-(diethylaminocarbonyl)-piperidinyl)	1-acenaphthenyl
337	S	1-(4-[(4-chlorophenyl)-phenylmethyl]-piperazinyl)	1-acenaphthenyl
360	S	1-(4-ethoxycarbonyl-piperidinyl)	1-acenaphthenyl
377	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	1-acenaphthenyl
382	R	1-imidazolyl	1-acenaphthenyl
388	S	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	1-(8-methyl-naphthyl)
445	R	2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl)	1-acenaphthenyl
465	S	1-piperidinyl	R-1-acenaphthenyl
691	S	1-morpholinyl	R-1-acenaphthenyl
692	S	1-pyrrolidinyl	R-1-acenaphthenyl
693	R	1-(4-ethoxycarbonyl-piperidinyl)	R-1-acenaphthenyl
694	R	1-(4-phenyl-piperidinyl)	R-1-acenaphthenyl
695	R	1-(3-hydroxymethyl-piperidinyl)	R-1-acenaphthenyl
696	R	1-(3-ethoxycarbonyl-piperidinyl)	R-1-acenaphthenyl
697	R	1-piperidinyl	R-1-acenaphthenyl
698	R	1-pyrrolidinyl	R-1-acenaphthenyl
699	S	1-(3,5-dimethyl-piperidinyl)	R-1-acenaphthenyl
700	S	1-(4-phenyl-piperidinyl)	R-1-acenaphthenyl
701	S	1-(4-ethoxycarbonyl-piperidinyl)	R-1-acenaphthenyl
702	S	1-(3-hydroxymethyl-piperidinyl)	R-1-acenaphthenyl
703	R	1-(3,5-dimethyl-piperidinyl)	R-1-acenaphthenyl
704	S	1-pyrrolidinyl	1-(8-methyl-naphthyl)

705	R	1-pyrrolidinyl	1-(8-methyl-naphthyl)
706	R	1-(3-(R)-hydroxy-pyrrolidinyl)	1-(8-methyl-naphthyl)
707	R	1-(3-hydroxy-piperidinyl)	1-(8-methyl-naphthyl)
708	R	1-(3-(R)-dimethylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
709	R	1-(4-hydroxy-piperidinyl)	1-(8-methyl-naphthyl)
710	R	1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
711	R	1-(4-t-butoxycarbonylamino-piperidinyl)	1-(8-methyl-naphthyl)
712	R	1-(3-hydroxy-pyrrolidinyl)	1-(8-methyl-naphthyl)
713	R	1-(4-pyrrolidinyl-piperidinyl)	1-(8-methyl-naphthyl)
714	R	1-(3-(S)-hydroxy-pyrrolidinyl)	1-(8-methyl-naphthyl)
715	R	1-((3-(S)-ethylamino)pyrrolidinyl)	1-(8-methyl-naphthyl)
716	R	1-(3-(R)-amino-pyrrolidinyl)	1-(8-methyl-naphthyl)
717	R	1-(3-(S)-amino-pyrrolidinyl)	1-(8-methyl-naphthyl)
718	R	1-(4-dimethylamino-piperidinyl)	1-(8-methyl-naphthyl)
719	R	1-(3-(R)-methylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
720	R	1-(3-(S)-methylamino-pyrrolidinyl)	1-(8-methyl-naphthyl)
721	R	1-(3-(N-methyl-N-t-butoxycarbonyl-amino)-pyrrolidinyl)	1-(8-methyl-naphthyl)

Table 5



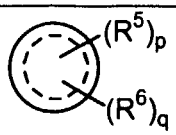
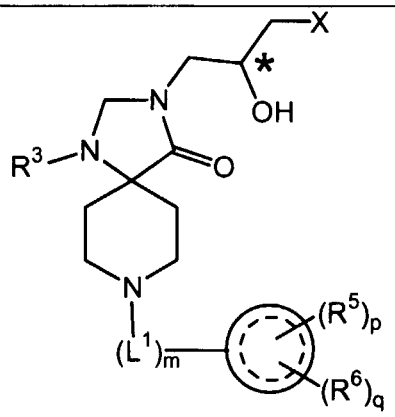
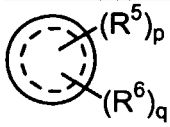
ID#	*	R^3	$(L^1)_m$	
100	R	4-fluorophenyl	CH_2	cyclooctyl
101	S	4-fluorophenyl	absent	1-acenaphthenyl
102	R	4-fluorophenyl	CH_2CH_2	phenyl
103	R	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
104	Rac	phenyl	absent	1-acenaphthenyl
179	R	phenyl	CH_2CH_2	2-(2-thienyl)-phenyl
447	R	4-fluorophenyl	CH_2	cyclooctyl

Table 6



ID #	*	X	R^3	$(L^1)_m$	
105	R	2-(3,4-dimethoxy phenyl)-ethyloxy	4-fluoro phenyl	CH_2	cyclooctyl
106	R	2-(3,4-dimethoxy phenyl)-ethyloxy	phenyl	CH_2CH_2	2-(2-thienyl)-phenyl
107	R	3-methylphenylthio	phenyl	CH_2CH_2	2-(2-thienyl)-phenyl
108	R	3-methylphenylthio	4-fluoro phenyl	CH_2	cyclooctyl

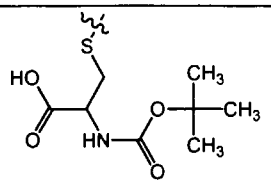
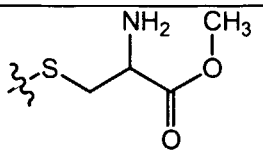
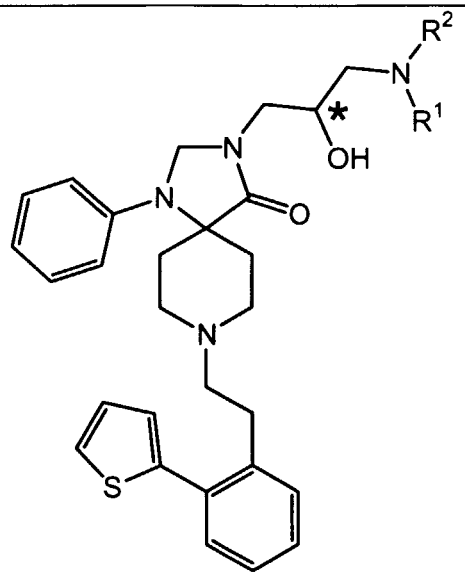
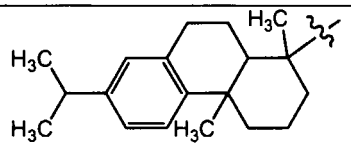
178	S		phenyl	CH_2CH_2	2-(2-thienyl)-phenyl
460	R		4-fluoro phenyl	CH_2	cyclooctyl

Table 7



ID No.	*	R^1	R^2
110	Rac	H	3-(4-morpholinyl)-n-propyl
111	S	H	3-(4-morpholinyl)-n-propyl
112	R	H	3-(4-morpholinyl)-n-propyl
113	S	H	3-chlorobenzyl
114	S	H	2-ethoxybenzyl
116	S	H	(2,5-dimethoxy-2,5-dihydro-fur-2-yl)-methyl
117	S	n-butyl	benzyl
118	S	H	2,5-difluorobenzyl
119	S	H	2-phenyl-ethyl

120	S	H	2-(5-bromo-pyridyl)
121	S	H	3-iodobenzyl
122	S	H	2,2,2-trifluoroethyl
123	S	H	3-nitrobenzyl
124	S	H	3,4-difluorobenzyl
125	S	H	3-bromobenzyl
126	S	H	4-chlorobenzyl
127	S	H	4-methoxybenzyl
128	S	H	3,4,5-trimethoxybenzyl
129	S	H	2-(2-thienyl)ethyl
130	S	H	3-methylbenzyl
131	S	H	2-methoxybenzyl
132	S	H	benzyl
133	S	H	4-bromobenzyl
134	S	H	3,5-di(trifluoromethyl) benzyl
135	S	H	2-(3-methoxyphenyl)ethyl
136	S	benzyl	2-phenylethyl
137	R	H	2-bromobenzyl
138	R	H	2-(4-bromophenyl)ethyl
139	R	H	4-(N,N-dimethylamino) benzyl
140	R	H	4-methylbenzyl
141	R	H	2-methylbenzyl
142	R	H	2-(6-fluoro-2-indolyl)ethyl
143	R	H	3-fluorobenzyl
144	R	H	3-methoxybenzyl
145	R	H	2-(4-methoxyphenyl)ethyl
146	R	H	2-trifluoromethylbenzyl
147	R	H	2-(4-imidazolyl)ethyl
148	R	H	3,5-dimethoxybenzyl
149	R	H	t-butyl
150	R	H	2-pyridyl-methyl
151	R	H	2-(3,4-dimethoxyphenyl) ethyl

152	R	H	2-fluorobenzyl
153	R	H	3-trifluoromethylbenzyl
154	R	H	4-pyridyl
155	R	H	4-trifluoromethoxybenzyl
156	R	H	2-phenyloxy-ethyl
157	R	H	1-naphthyl-methyl
158	R	H	4-fluorobenzyl
159	R	H	4-trifluoromethylbenzyl
161	R	H	4-pyridyl-methyl
162	R	H	2,4-dichlorobenzyl
163	S	H	
164	S	benzyl	benzyl
167	S	H	1-(3,4-methylene dioxyphenyl)methyl
168	S	benzyl	ethoxycarbonylmethyl
169	S	H	2-phenyl-cyclopropyl
170	S	H	4-methoxycarbonylbenzyl
171	S	benzyl	2-(N,N-dimethylamino)ethyl
173	S	methyl	benzyl
174	S	ethyl	benzyl
175	R	benzyl	carboxymethyl
176	R	benzyl	2-(N,N-dimethylamino)ethyl
177	R	n-butyl	benzyl
180	R	H	2-phenyl-cyclopropyl
182	R	H	4-methoxycarbonylbenzyl
187	R	H	2-(2,5-dimethoxy-2,5-dihydro-fur-2-yl)-methyl
189	R	H	2,4-dimethoxybenzyl
190	R	H	4-biphenyl
191	R	benzyl	ethoxycarbonylmethyl

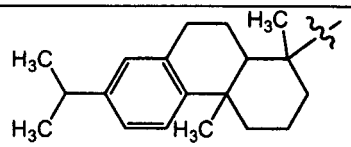
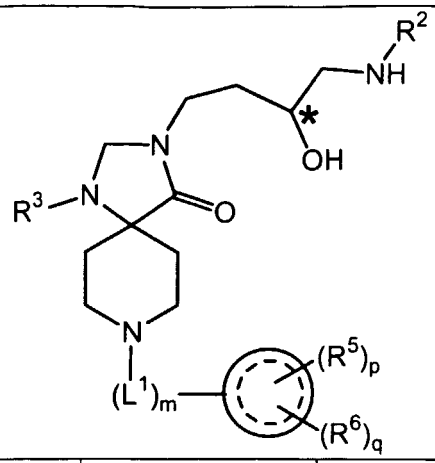
192	R	H	4-methoxybenzyl
193	S	H	2-methylbenzyl
194	S	H	3,5-dimethoxybenzyl
197	S	H	4-pyridyl
198	S	H	2,4-dichlorobenzyl
203	S	H	3,4-dimethoxybenzyl
204	R	H	4-bromobenzyl
205	R	H	3-methylbenzyl
206	R	H	2-(2-thienyl)-ethyl
208	S	H	3-nitrobenzyl
209	S	H	2-bromobenzyl
210	S	H	2-(4-imidazolyl)-ethyl
211	S	H	2-(phenoxy)-ethyl
215	S	H	2,3-dimethoxybenzyl
216	S	H	
217	S	H	adamantanyl
218	S	H	n-propyl
219	S	n-propyl	n-propyl
220	S	benzyl	benzyl
224	S	H	3-methoxybenzyl
225	S	H	3-pyridyl-methyl
227	S	H	2,4-difluorobenzyl
228	R	H	2-methoxybenzyl
229	S	H	3-(phenyl)-n-propyl
230	S	benzyl	2-phenylethyl

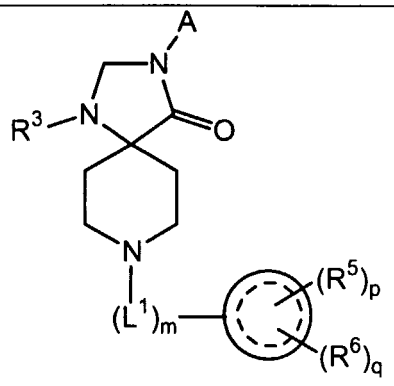
Table 8



ID #	*	R^2	R^3	$(L^1)_m$	$(R^5)_p$, $(R^6)_q$
722	S	H	4-fluorophenyl	absent	R-1-acenaphthenyl

Representative intermediates in the preparation of the compounds of the present invention are as listed in Tables 9 and 10. Wherein Table 9, A is listed as oxarinyl-methyl with no indication of the stereo-configuration, the oxarinyl-methyl group was present as racemate.

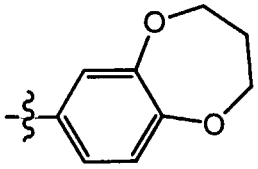
Table 9

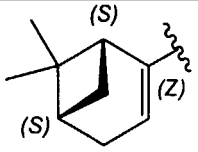
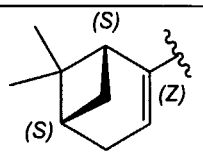
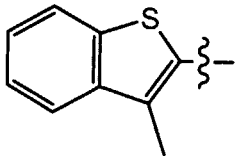


ID #	A	R^3	$(L^1)_m$	$(R^5)_p$, $(R^6)_q$
500	H	4-fluorophenyl	absent	1-acenaphthenyl
501	H	4-fluorophenyl	CH_2-CH(CH_3)-CH_2	phenyl

502	H	4-fluorophenyl	CH_2CH_3	
503	H	4-fluorophenyl	CH_2CH_2	phenyl
504	H	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
505	H	4-fluorophenyl	C(O)O-t-butyl	
506	H	4-fluorophenyl	CH_2	2-naphthyl
507	H	4-fluorophenyl	CH_2	1-naphthyl
508	H	4-fluorophenyl	CH_2	4-chlorophenyl
521	H	4-fluorophenyl	CH_2	4-quinolinyl
522	H	4-fluorophenyl	CH_2	8-quinolinyl
544	H	4-fluorophenyl	absent	1,3,4-trihydro-2-naphthyl
546	H	4-fluorophenyl	CH_2	5-phenyl-2-thienyl
547	H	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
548	H	4-fluorophenyl	CH_2	1-(4-methyl-naphthyl)
549	H	4-fluorophenyl	absent	2-hydroxy-cycloheptyl
551	H	4-fluorophenyl	CH_2	1-(2-methyl-naphthyl)
555	H	4-fluorophenyl	absent	R-1-acenaphthenyl
556	H	4-fluorophenyl	absent	S-1-acenaphthenyl
509	oxiranyl-methyl	phenyl	absent	1-acenaphthenyl
510	R-oxiranyl-methyl	4-fluorophenyl	absent	4-n-propyl-cyclohexyl
511	R-oxiranyl-methyl	4-fluorophenyl	CH_2CH_2	phenyl
512	oxiranyl-methyl	4-fluorophenyl	absent	1-acenaphthenyl

513	R-oxiranyl-methyl	4-fluorophenyl	CH_2	4-chlorophenyl
514	R-oxiranyl-methyl	4-fluorophenyl	CH_2	1-naphthyl
516	R-oxiranyl-methyl	4-fluorophenyl	C(O)O-t-butyl	absent
517	S-oxiranyl-methyl	4-fluorophenyl	C(O)O-t-butyl	absent
518	oxiranyl-methyl	phenyl	CH_2CH_2	2-(2-thienyl) phenyl
519	S-oxiranyl-methyl	phenyl	CH_2CH_2	2-(2-thienyl) phenyl
520	R-oxiranyl-methyl	phenyl	CH_2CH_2	2-(2-thienyl) phenyl
540	R-oxiranyl-methyl	4-fluorophenyl	CH_2	cyclooctyl
541	R-oxiranyl-methyl	4-fluorophenyl	CH_2	5-phenyl-2-thienyl
542	S-oxiranyl-methyl	4-fluorophenyl	CH_2	2-naphthyl
543	S-oxiranyl-methyl	4-fluorophenyl	CH_2CH_3	absent
550	S-oxiranyl-methyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
552	methoxy-carbonyl-methyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
553	R-oxiranyl-methyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)
554	R-2,3-dihydroxy-n-propyl	4-fluorophenyl	CH_2	1-(8-methyl-naphthyl)

564	S-oxiranyl-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
565	R-oxiranyl-methyl	4-fluorophenyl	absent	R-1-acenaphthenyl
566	S-oxiranyl-methyl	4-fluorophenyl	absent	S-1-acenaphthenyl
567	R-oxiranyl-methyl	4-fluorophenyl	absent	S-1-acenaphthenyl
568	2R-hydroxy-3-ethoxy-n-propyl	4-fluorophenyl	absent	1-acenaphthenyl
569	2R-hydroxy-3-ethoxy-n-propyl	4-fluorophenyl	absent	S-1-acenaphthenyl
570	2S-hydroxy-3-ethoxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
571	2R-hydroxy-3-ethoxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
572	H	4-fluorophenyl	CH_2	
573	H	4-fluorophenyl	CH_2	3-(2H)-chromenyl
576	oxiranyl-methyl	phenyl	absent	1-acenaphthenyl
578	R-oxiranyl-methyl	4-fluorophenyl	CH_2	2-trifluoromethyl-6-chloro-phenyl

579	3-chloro-2S-hydroxy-n-propyl	4-fluorophenyl	absent	R-1-acenaphthenyl
580	S-oxiranyl-methyl	4-fluorophenyl	CH_2	cyclooctyl
581	H	phenyl	CH_2CH_2	2-(2-thienyl)-phenyl
582	H	4-fluorophenyl	CH_2	cyclooctyl
583	H	4-fluorophenyl	CH_2	2,3,4,5,6-pentamethyl-phenyl
584	R-oxiranyl-methyl	4-fluorophenyl	CH_2	2,3,4,5,6-pentamethyl-phenyl
723	R-oxiranyl-ethyl	4-fluorophenyl	absent	R-1-acenaphthenyl
725	R-oxiranyl-methyl	4-fluorophenyl	CH_2	2,3,4,5,6-pentamethylphenyl
726	H	4-fluorophenyl	CH_2	
727	R-oxiranyl-methyl	4-fluorophenyl	CH_2	
728	H	4-fluorophenyl	CH_2	1-(8-methyl-1,2,3,4-tetrahydro-naphthyl)
729	H	4-fluorophenyl	$CH(CH_3)$	

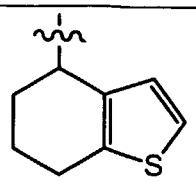
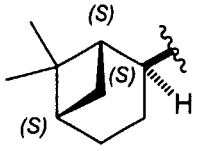
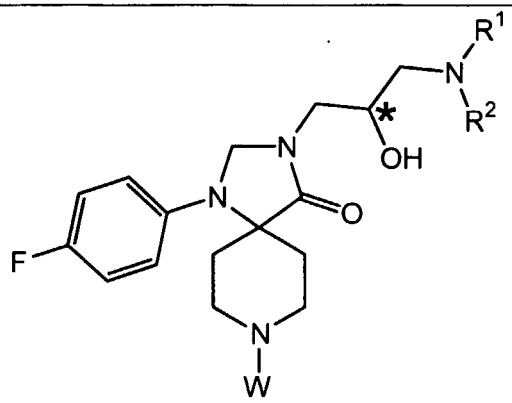
730	H	4-fluorophenyl	absent	
731	S-oxiranyl-methyl	4-fluorophenyl	absent	cyclooctyl
732	H	4-fluorophenyl	CH_2	
733	H	4-fluorophenyl	CH_2	1-[8-methoxy)-naphthyl]
734	H	4-fluorophenyl	CH_2	1-[8-hydroxymethyl)-naphthyl]
735	H	4-fluorophenyl	absent	cyclooctyl

Table 10



ID #	*	R^1	R^2	W
523	R	ethyl	4-methylbenzyl	H
524	R	H	2-(4-morpholinyl)-ethyl	H
525	R	t-butyl	benzyl	H
526	R	H	2-(3,4-dimethoxy-phenyl)-ethyl	H

527	R	H	2-(3,4-methylenedioxy phenyl)-ethyl	H
528	R	H	2-(2-nitro-4,5-dimethoxy-phenyl)-ethyl	H
529	S	ethyl	4-methylbenzyl	H
530	S	H	2-(4-morpholinyl)-ethyl	H
531	S	t-butyl	benzyl	H
532	S	H	2-(3,4-dimethoxy-phenyl)-ethyl	H
533	S	H	2-(3,4-methylenedioxy phenyl)-ethyl	H
534	S	H	2-(2-nitro-4,5-dimethoxy-phenyl)-ethyl	H
535	S	ethyl	4-methylbenzyl	t-butoxycarbonyl
536	R	ethyl	4-methylbenzyl	ethyl
537	R	H	2-(4-morpholinyl)-ethyl	ethyl
538	R	t-butyl	benzyl	ethyl
539	R	H	2-(3,4-dimethoxy-phenyl)-ethyl	ethyl

Molecular weights for representative compounds of the present invention exemplified in Tables 1-10 above were measured using a Micromass Platform LC-Electrospray Mass Spectrometer, Chemical Ionization Spectrometer HP5989A or Agilent LC/MSD Electrospray Mass Spectrometer with results as listed in Table 11.

Table 11

ID#	Theor. MW	M/e[MH+]
1	559.77	560.8
2	596.78	597.7
3	672.73	673.6
4	540.72	541.7
5	615.63	617.9
6	610.81	611.8
7	572.71	573.3

8	596.78	597.5
9	598.8	599.5
10	580.78	581.5
11	550.76	551.5
12	572.71	573.5
13	602.60	604.3
14	566.76	567.5
15	615.60	617.4
16	672.73	673.5
17	594.85	595.5
18	550.76	551.5
19	588.76	589.5
20	615.63	617.4
21	571.18	571.5
22	596.78	597.5
23	581.73	582.5
24	537.72	538.4
25	596.78	597.2
26	556.79	557.4
27	550.76	552.4
28	540.72	541.5
29	604.73	605.5
30	629.65	630.5
31	605.62	607.3
32	537.72	538.4
33	604.73	605.4
34	566.76	567.5
35	566.76	567.7
36	523.69	523.9
38	610.81	611.5
39	537.72	538.5
40	586.79	587.4
41	550.76	551.4
42	551.75	551.5
43	626.81	627.4
44	615.63	616.4
45	596.78	597.3
46	605.62	607.4
47	587.70	588.3
48	638.70	639.3
49	610.81	611.4
50	539.63	540.3
51	590.74	591.3
52	621.00	622.0
53	569.00	570.0
54	620.88	621.5
55	606.70	607.3
56	620.80	621.3

57	578.81	579.5
58	558.74	559.3
59	592.84	593.4
60	572.77	573.3
61	588.00	589.0
62	602.00	603.0
63	607.28	608.3
64	592.84	593.5
65	640.88	641.5
66	659.81	660.1
67	597.86	598.2
68	649.85	650.1
69	613.86	614.3
70	498.68	499.5
71	716.38	717.4
72	562.77	563.5
73	615.83	616.4
74	622.82	623.2
75	544.75	545.4
76	605.84	606.2
78	649.89	650.2
79	750.01	751.5
100	592.77	593.8
101	620.70	621.3
102	572.70	573.3
103	592.77	593.3
104	602.70	603.0
105	611.79	612.4
106	655.86	656.4
107	597.84	598.4
108	553.78	554.6
110	617.85	618.3
111	617.85	618.3
112	617.85	618.3
113	615.24	615.3
114	624.85	625.3
115	606.83	607.3
116	632.82	633.3
117	636.90	637.4
118	616.78	617.3
119	594.80	595.3
120	646.65	648.2
121	706.68	707.2
122	572.69	573.3
123	625.79	626.3
124	616.77	617.3
125	659.68	661.2
126	615.30	615.3

127	610.82	611.3
128	670.87	671.3
129	600.85	601.2
130	594.82	595.3
131	610.82	611.3
132	580.79	581.2
133	659.69	661.2
134	716.79	717.2
135	624.85	625.3
136	684.94	685.3
137	659.69	661.2
138	673.72	675.3
139	623.86	624.4
140	594.82	595.4
141	594.82	595.4
142	651.85	652.3
143	598.78	599.3
144	610.82	611.3
145	624.85	625.3
146	648.80	649.3
147	584.76	585.3
148	640.85	641.3
149	546.77	547.3
150	581.78	582.3
151	654.87	655.5
152	598.78	599.3
153	648.79	649.3
154	567.75	568.3
155	664.79	665.3
156	610.82	611.3
157	630.85	631.3
158	598.78	599.3
159	648.80	649.3
160	659.89	660.4
161	581.78	582.3
162	649.68	651.1
163	759.11	759.1
164	670.82	671.4
165	659.89	660.5
166	666.88	667.4
167	624.80	625.4
168	666.88	667.4
169	606.83	607.5
170	638.83	639.4
171	651.92	653.0
173	594.80	595.8
174	608.85	609.9
175	638.83	639.6

176	651.92	652.9
177	636.90	637.6
178	694.91	695.8
179	636.90	637.6
180	606.83	607.9
181	666.88	667.8
182	638.83	639.8
183	544.76	545.7
187	632.82	633.9
188	630.85	631.9
189	640.85	641.9
190	642.86	643.8
191	666.88	667.8
192	610.82	611.9
193	594.82	595.8
194	640.85	641.9
197	567.75	568.8
198	649.68	651.6
203	640.85	641.7
204	659.69	662.0
205	594.82	595.9
206	600.85	601.7
208	625.79	626.8
209	659.69	661.2
210	584.79	585.8
211	610.82	611.8
215	640.85	641.7
216	759.11	759.7
217	638.92	639.8
218	532.75	533.6
219	574.83	575.9
220	670.92	671.7
224	610.82	611.8
225	581.78	582.7
227	616.78	617.7
228	610.82	611.8
229	608.85	609.7
230	684.94	685.7
250	608.79	609.3
251	575.72	576.3
252	594.76	595.3
253	626.76	627.3
254	610.72	611.2
255	671.76	672.3
256	640.79	641.4
257	638.77	639.3
258	594.76	595.3
259	575.72	576.3

260	608.79	609.3
261	626.76	627.3
262	610.72	611.2
263	640.78	641.4
264	579.15	579.3
265	560.10	560.2
266	593.17	593.3
267	611.15	691.2
268	595.10	595.2
269	656.14	656.2
270	625.17	625.3
271	622.72	623.2
275	652.80	653.4
276	683.79	684.3
279	650.88	651.3
280	628.88	629.2
281	566.77	567.5
282	743.95	744.1
283	565.75	566.4
284	605.85	605.9
285	604.86	605.3
289	634.89	635.3
290	648.91	649.2
291	662.94	663.3
292	658.84	659.2
293	607.80	608.3
294	626.84	627.3
295	634.82	635.4
296	650.80	651.3
298	587.74	588.3
299	620.82	621.4
300	638.79	639.3
305	652.82	653.3
307	624.76	625.3
308	609.71	610.3
309	619.79	620.3
310	626.78	627.3
311	554.67	555.4
312	690.61	691.2
313	668.86	669.3
314	600.69	601.3
315	643.61	643.6
316	599.15	599.2
317	594.74	595.3
318	594.74	595.3
319	700.71	701.2
320	654.79	655.3
321	582.70	583.3

322	594.74	595.3
323	608.76	609.3
324	624.76	625.3
325	578.74	579.3
326	592.76	593.4
327	551.67	552.3
328	648.71	649.3
329	594.74	595.3
330	578.74	579.0
331	624.76	625.3
332	633.82	634.3
333	687.79	688.3
334	625.84	626.4
335	677.83	678.3
336	641.84	642.5
337	744.36	744.3
338	643.90	644.4
339	652.82	653.4
340	652.82	653.4
341	578.74	579.3
342	600.69	601.3
343	633.60	633.2
344	632.71	634.0
345	564.71	565.3
346	582.70	583.3
347	632.71	634.0
348	622.75	623.2
349	624.76	625.3
350	599.15	599.2
351	608.76	609.3
352	643.10	643.2
353	578.74	579.3
354	584.72	583.3
355	643.61	645.2
356	608.72	609.0
358	600.69	601.0
360	614.77	615.0
362	654.84	655.3
364	593.75	594.2
365	657.63	659.2
366	565.70	566.2
367	654.79	655.3
368	633.60	635.2
370	609.71	610.3
371	614.77	615.3
372	584.76	595.3
373	632.71	633.3
374	743.03	743.6

375	579.72	580.3
376	565.70	566.2
377	650.80	651.3
378	551.67	552.2
379	551.67	552.2
380	581.70	582.2
381	551.67	552.3
382	525.63	526.2
383	565.70	566.2
385	640.81	641.4
386	640.81	641.4
387	589.76	590.4
388	652.82	653.4
389	622.83	623.4
390	624.76	625.3
391	654.83	655.3
392	596.75	597.3
393	553.69	554.2
394	608.81	609.4
395	622.83	623.4
396	589.76	590.4
398	596.75	597.3
399	654.83	655.3
418	624.76	625.3
419	551.67	552.3
420	474.58	475.2
421	551.67	552.3
422	476.6	477.3
423	502.64	503.3
424	474.58	475.2
425	488.61	489.3
426	474.58	475.2
427	488.61	489.3
428	502.64	503.3
429	516.66	517.3
430	474.58	475.2
431	488.61	489.3
432	502.64	503.3
433	516.66	517.3
434	516.66	517.3
435	502.64	503.3
436	516.66	517.3
437	488.61	489.3
438	476.6	477.3
439	504.65	505.4
440	518.68	519.3
441	504.65	505.4
442	518.68	519.3

443	504.61	505.2
444	518.64	519.3
445	650.80	651.3
446	622.75	623.2
447	592.78	593.4
448	594.74	595.3
451	743.95	744.1
452	580.75	581.5
453	446.61	447.9
454	502.72	503.2
455	701.95	702.0
456	661.19	662.5
457	693.19	694.0
458	591.05	592.0
459	676.20	677.4
460	564.77	565.2
461	683.79	684.3
462	606.79	607.3
463	580.71	581.3
464	593.75	594.3
465	542.70	543.3
500	401.49	402.2
501	367.47	368.2
502	277.34	278.2
503	353.44	354.2
504	373.52	374.2
505	349.41	372.0
506	389.48	390.1
507	389.48	390.1
508	373.86	374.1
509	439.56	440.2
510	409.51	410.2
511	429.58	430.3
512	457.55	458.3
513	429.93	430.2
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517	405.47	428.3
518	473.65	474.1
519	473.65	474.1
520	473.65	474.1
521	390.45	391.2
522	390.45	391.0
523	454.58	455.0
524	435.54	436.0
525	468.61	469.0
526	486.58	487.0
527	470.54	471.0

528	531.58	532.0
529	454.48	544.0
530	435.54	436.0
531	468.61	469.0
532	486.58	488.0
533	470.54	471.0
534	531.58	532.0
535	554.70	555.3
536	482.65	483.3
537	463.60	464.3
538	496.67	497.4
539	514.65	515.2
540	429.58	430.5
541	477.61	478.2
542	445.54	446.3
543	333.41	334.2
544	379.48	380.2
546	421.54	422.1
547	403.50	404.2
548	403.50	404.2
549	361.46	362.3
550	459.57	460.2
551	403.50	404.2
552	475.57	476.2
553	459.57	460.2
554	477.58	478.2
555	401.49	402.1
556	401.49	402.1
564	457.55	458.3
565	457.55	458.3
566	457.55	458.3
567	457.55	548.3
568	503.62	504.3
569	503.62	504.3
570	503.62	504.3
571	503.62	504.3
572	411.48	412.2
573	393.47	394.2
576	439.56	458.3
578	497.92	498.9
579	494.01	494.2
581	417.58	418.1
582	373.52	374.1
583	409.55	410.5
584	465.62	466.1
600	550.68	551.7
601	693.87	694.9
602	568.67	569.7

603	610.74	611.7
604	564.71	565.7
605	593.75	594.8
606	514.65	515.7
607	696.76	697.8
608	625.59	626.6
609	639.62	640.6
610	717.82	718.8
611	565.7	566.7
612	565.7	566.7
613	565.7	566.7
614	570.73	571.7
615	692.76	693.8
616	432.59	433.6
617	509.67	510.7
618	533.7	534.7
619	456.61	457.6
620	446.61	447.6
621	523.7	524.7
622	692.76	693.8
623	432.59	433.6
624	488.69	489.7
625	567.71	568.7
626	701.03	702.0
627	509.67	510.7
628	580.75	581.8
629	526.7	527.7
630	658.86	659.9
631	576.72	577.7
632	496.65	497.7
633	531.76	532.8
634	504.69	505.7
635	504.69	505.7
636	531.76	532.8
637	532.66	533.7
638	559.73	560.7
639	532.73	533.7
640	474.65	475.7
641	546.69	547.7
642	532.66	533.7
643	532.66	533.7
644	546.69	547.7
645	690.74	691.7
646	690.74	691.7
647	559.73	560.7
648	490.63	491.6
649	534.68	535.7
650	548.71	549.7

651	534.68	535.7
652	235.13	236.1
653	430.5	431.5
654	545.71	546.7
655	547.72	548.7
656	547.72	548.7
657	517.74	518.7
658	545.77	546.8
659	474.65	475.7
660	490.63	491.6
661	533.7	534.7
662	631.8	632.8
663	578.74	579.7
664	529.75	530.8
665	633.81	634.8
666	561.75	562.8
667	633.80	634.2
668	578.74	579.7
669	564.71	565.7
670	724.73	725.7
671	694.74	695.7
672	742.79	743.8
673	726.74	727.7
674	709.76	710.8
675	610.82	611.8
676	578.82	579.8
677	602.84	603.8
678	564.74	565.7
679	645.82	646.8
680	647.84	648.8
681	547.72	548.7
682	664.67	665.7
683	761.71	762.7
684	688.69	689.7
685	600.58	601.6
686	715.76	716.8
687	688.66	689.7
688	578.73	579.7
689	608.8	609.8
690	702.36	703.4
691	544.68	545.7
692	528.68	529.7
693	614.77	615.8
694	618.8	619.8
695	572.73	573.7
696	614.77	615.8
697	542.7	543.7
698	528.68	529.7

699	570.76	571.8
700	618.8	619.8
701	614.77	615.8
702	572.73	573.7
703	570.76	571.8
704	530.69	531.7
705	530.69	531.7
706	546.69	547.7
707	560.72	561.7
708	573.76	574.8
709	560.72	561.7
710	645.82	646.8
711	659.85	660.9
712	546.69	547.7
713	613.83	614.8
714	546.60	647.7
715	573.76	574.8
716	545.71	546.7
717	545.71	546.7
718	587.79	588.8
719	559.73	560.7
720	559.73	560.7
721	659.85	660.9
722	488.61	489.6
723	471.58	472.6
725	465.62	466.6
726	383.51	384.5
727	439.58	440.6
728	407.54	408.5
729	423.56	424.6
730	385.51	386.5
731	415.56	416.6
732	385.53	386.4
733	433.53	434.5
734	419.5	420.5
735	359.49	360.5

The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable

for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 5 to about 1000 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran,

sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

The method of treating disorders mediated by the ORL-1 receptor described in the present invention may also be carried out using a pharmaceutical composition comprising any of the compounds as defined herein and a pharmaceutically acceptable carrier. The pharmaceutical composition may contain between about 1 mg and 1000 mg, preferably about 10 to 500 mg, of the compound, and may be constituted into any form suitable for the mode of administration selected. Carriers include necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. Compositions suitable for oral administration include solid forms, such as pills, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders, and liquid forms, such as solutions, syrups, elixers, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

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 of ordinary skill 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.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-

lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The liquid forms may include suitably flavored suspending or dispersing agents such as the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phophatidylcholines.

The compound of the present invention can also be administered via transdermal skin patches well known to those of ordinary skill 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.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamidephenol, polyhydroxyethylaspartamidephenol, or polyethyl-eneoxidepolylysine substituted with palmitoyl residue. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals,

polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Compounds of this invention may be administered in any of the foregoing compositions and according to dosage regimens established in the art whenever treatment of disorders mediated by the ORL-1 receptor is required.

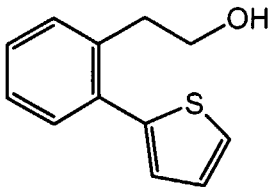
The daily dosage of the products may be varied over a wide range from 1 to 1,000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.5, 1.0, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.01 mg/kg to about 30 mg/kg of body weight per day. Preferably, the range is from about 0.1 mg/kg to about 10 mg/kg of body weight per day, and especially from about 0.5 mg/kg to about 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 4 times per day.

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

The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Example 1

2-Thienylphenyl-2-ethanol



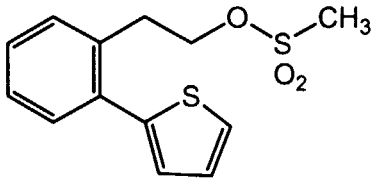
3-Bromophenethyl alcohol (4 ml, 29.8 mmol) was dissolved in 1,2-dimethoxyethane (225 mL) and mixed with tetrakistriphenylphosphine palladium[0] (2.6 g, 2.25 mmol) at room temperature. The reaction mixture was then added to a solution of 2-thienyl-boronic acid (12.6 g, 99 mmol) and 1N $NaHCO_3$ (90 mL). The reaction mixture was heated to reflux under nitrogen atmosphere for 48 hours. The reaction mixture was partitioned with water and ethyl acetate. The organic layer was dried with $MgSO_4$, filtered through a plug of silica and the solvent was evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (30% EtOAc/hexane) to yield the title compounds as an oil.

MS (chemical ionization) = 221 ($M+NH_4$)

^1H NMR (300 MHz, $CDCl_3$) δ 1.3 (t, 1H), 3.0 (t, 2H), 3.75 (q, 2H), 7.0-7.4 (m, 7H)

Example 2

Methane sulfonic acid 2-(2-thien-2-yl-phenyl)-ethyl ester



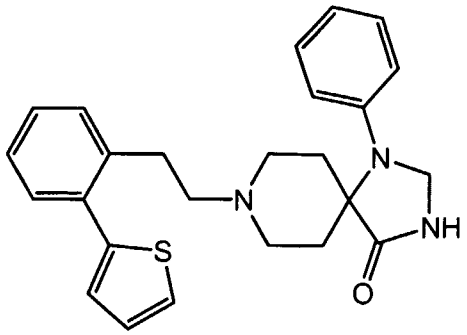
2-Thienylphenylethanol (13.6 mmol) and triethylamine (2.4 mL, 17.1 mmol) were dissolved in dichloromethane (50 mL). Methanesulfonylchloride (1.1 mL, 14 mmol) was then added slowly. The reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was carefully partitioned with water and dichloromethane. The organic layer was dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield the title compounds, which was used without further purification.

MS (chemical ionization) = 300 ($M+NH_4$), 283 (MH+), 187,

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.8 (s, 3H), 3.2 (t, 2H), 4.3 (t, 2H), 7.0 (m. 1H), 7.1 (m, 1H), 7.2-7.5 (m, 5H)

Example 3

1-Phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #581



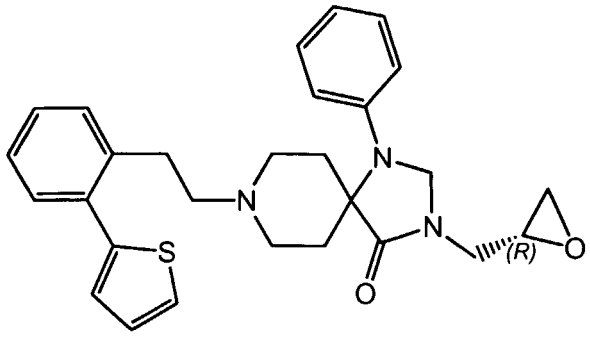
Methane sulfonic acid 2-(2-thien-2-yl-phenyl)-ethyl ester (23.14 mmol) was combined in NMP (100 mL) with 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (5.08 g, 22 mmol) and DIPEA (5.11 mL, 27.8 mmol) in a reaction tube which was sealed and heated to 70°C overnight. The reaction mixture was partitioned with water and ethyl acetate. The organic layer was dried with $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5% methanol/CH_2Cl_2) to yield the title compound as a solid.

MS (electrospray) = 418.1 (MH+), 313.0

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.5 (d, 2H), 2.4 (m,4 H), 2.6 (m, 4H), 2.85 (m, 2H), 4.55 (s, 2H), 6.7-6.8 (m, 3H), 7.1-7.4 (m, 8H), 7.6 (s, 1H), 8.65 (s, 1H)

Example 4

(R)-3-Oxiranylmethyl-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #520



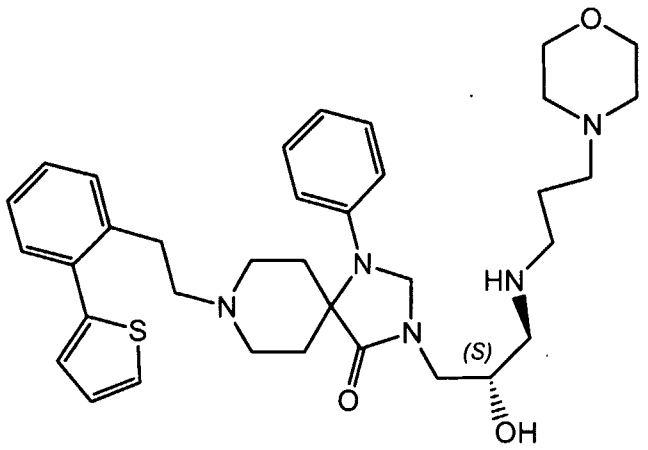
1-Phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-4-one (0.7 g, 1.68 mmol) was dissolved in NMP (50 mL). To the mixture was then added sodium hydride (60% in mineral oil, 0.1, 2.52 mmol) and the reaction mixture stirred for 1 hour. S-(+)-epichlorohydrin (0.15 mL, 1.9 mmol) was then added to the reaction mixture. The reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned with saturated sodium bicarbonate and ethyl acetate. The organic layer was then partitioned with water. The organic layer was dried with $MgSO_4$, filtered and the solvent was evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (80% EtOAc/hex) to yield the title compound as an oil.

MS (electrospray) = 474.1 (MH+)

^1H NMR (300 MHz, $CDCl_3$) δ 1.6 (t, 2H), 2.5-3.0 (m, 12H), 3.1-3.2 (m, 2H), 4.05 (d, 1H), 4.7 (d, 1H), 4.8 (d, 1H), 6.8 (m, 2H), 7.0 (m, 1H), 7.2-7.4 (m, 9H).

Example 5

3-[2-(S)-Hydroxy-3-(3-morpholin-4-yl-propylamino)-propyl]-1-phenyl-8-[2-(2-thien-2-yl-phenl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #111



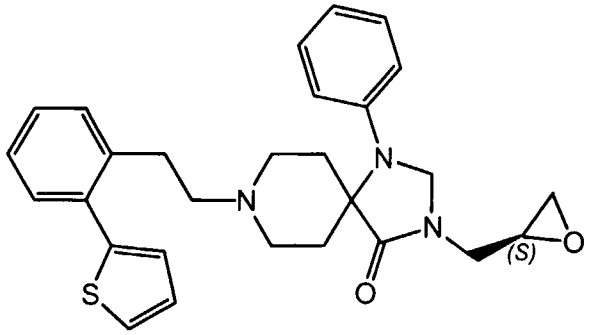
3-(R)-Oxiranylmethyl-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triaza-spiro[4.5]decan-4-one (0.1 g, 0.21 mmol) was dissolved in absolute ethanol (2 mL), mixed with 3-aminopropyl morpholino (90 µl, 0.63 mmol) and heated to 70°C overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (AcCN/water) to yield the title compounds as a trifluoroacetate salt, as a solid.

MS (electrospray) = 618.3 (MH+)

^{1}H NMR (300 MHz, CD_3OD) δ 2.0 (d, 2H), 2.2 (m, 2H), 2.72-2.88 (m, 2H), 3.0-4.3 (m, 23H), 4.8-5.05 (m, 6H), 6.8-7.5 (m, 12H).

Example 6

(S)-3-Oxiranylmethyl-1-phenyl-8-[2-(2-thienyl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one Compound #519



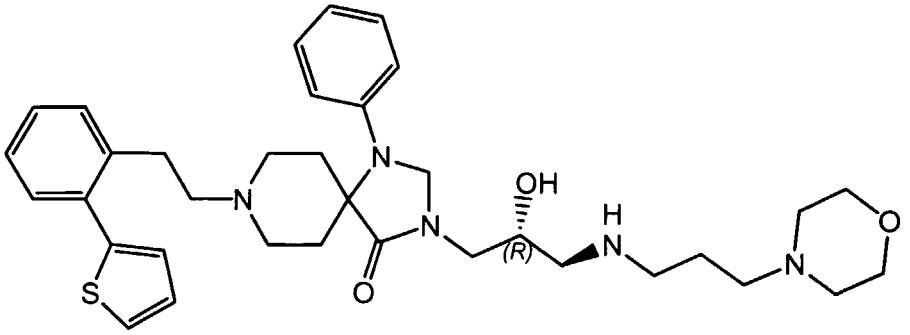
1-Phenyl-8-[2-(2-thienyl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one (0.13 g, 0.3 mmol) was dissolved in NMP (10 mL). To the mixture was then added sodium hydride (60% in mineral oil, 31 mg, 0.8 mmol) and the reaction mixture stirred for 1 hour. R-(-)-epichlorohydrin 927µL, 0.35 mmol) was then added to the reaction mixture, which was then stirred overnight at room temperature. The reaction mixture was partitioned with saturated sodium bicarbonate and ethyl acetate. The organic layer was then partitioned with water. The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (80% EtOAc/hexanes) to yield the title compound as an oil.

MS (electrospray) = 474.1 (MH+)

^1H NMR (300 MHz, $CDCl_3$) δ 1.65 (t, 2H), 2.0 (q, 1H), 2.4 (t, 1H), 2.5-3.0 (m, 11H), 3.2 (m, 1H), 3.3(t, 1H), 4.0 (d, 1H), 4.7 (d, 1H), 4.8 (d, 1H), 6.9 (m, 2H), 7.0 (m, 1h), 7.15-7.4 (m, 9H).

Example 7

3-[2-(R)-hydroxy-3-(3-morpholin-4-yl-propylamino)-propyl]-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one Compound #112



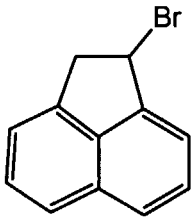
3-(S)-Oxiranylmethyl-1-phenyl-8-[2-(2-thien-2-yl-phenyl)-ethyl]-1,3,8-triazaspiro[4.5]decan-4-one (0.13 g, 0.27 mmol) was dissolved in absolute ethanol (2 mL), mixed with 3-aminopropylmorpholino (100 µL, 0.68 mmol) and heated with stirring at 70°C overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (Acetonitrile/water) to yield the title compound as a trifluoroacetate salt as a solid.

MS (electrospray) = 618.3 (MH+)

^{1}H NMR (300 MHz, CD_3OD) δ 2.0 (d, 2H), 2.2 (m, 2H), 2.75-2.9 (m, 2H), 3.0-4.3 (m, 23H), 4.8-5.05 (m, 6H), 6.8-7.5 (m, 12H).

Example 8

1-bromo-acenaphthene



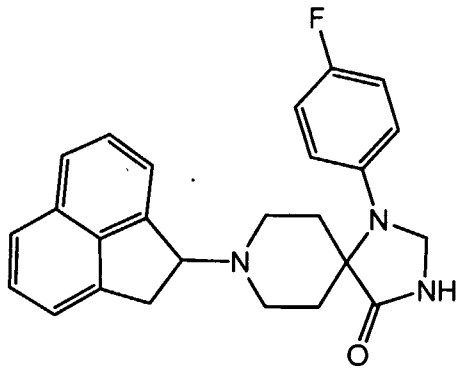
Acenaphthen-1-ol (88 mol) was dissolved in diethyl ether (150 mL) and cooled down to 0°C. Phosphorous tribromide (3.2 mL, 35 mmol) was then added slowly under nitrogen atmosphere. The reaction mixture was stirred for 30 minutes at room temperature and cooled to 0°C. The reaction mixture was partitioned with water and diethyl ether. The organic layer was dried over

Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield the title compound as a yellow solid.

Example 9

8-Acenaphthen-1-yl-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one

Compound # 500



1-Bromo-acenaphthene (20.5 g, 87.9 mmol) and 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (9.15 g, 36.6 mmol) were dissolved in N, N-dimethylformamide (190 mL). Potassium carbonate (15.15 g, 110 mmol) was then added and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 18 hours. The reaction mixture was partitioned with water and diethyl ether. The title compound precipitated from the organic layer as an off-white solid.

^1H NMR (300 MHz, $CDCl_3$) δ7.68-7.66 91H,m), 7.60 (1H, d, J=8.2 Hz), 7.53-7.49 (2H, m), 7.43 (1H, t, J = 8.1 Hz), 7.26 (1H, d, J = 7.8 Hz), 7.04-6.94 (4H, m), 6.67 (1H, br, s), 4.95 (1H, br, s), 4.66-4.63 (2H, m), 3.51 (1H, d), 3.34 (1H, dd J = 7.6 and 17.5 Hz), 3.13-2.94 (2H, m), 2.83 (1H, br, s), 2.43 (1H, br, a), 2.24 (1H, m), 1.80-1.66 (3H, m)

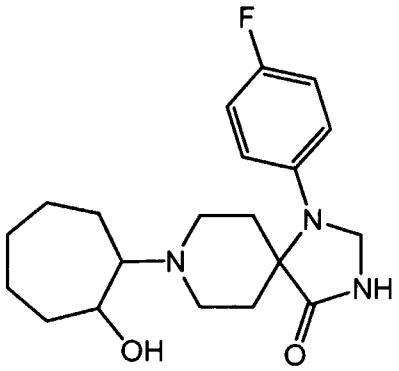
MS (ES^+) m/z 402.1 $(M+H)^+$

Chiral resolution: The racemate prepared as described above was resolved using a CHIRALCEL OD-H column with methanol as mobile phase and generated the two pure enantiomers R (RT=6.174 minutes, ee>99%) and S (RT=10.175 minutes, ee>99%).

Example 10

1-(4-fluorophenyl)-8-(2-hydroxy-cycloheptyl)-1,3,8-triazaspiro[4.5]decan-4-one

Compound #549



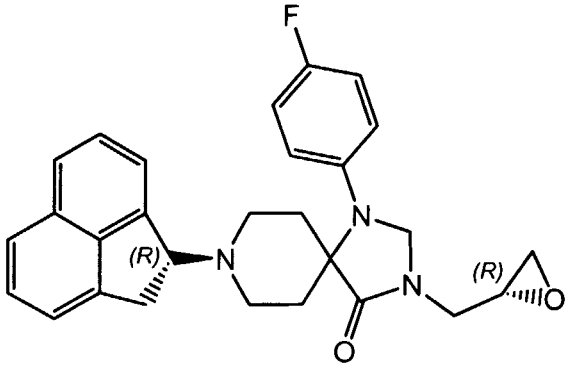
1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (0.15 g, 0.6 mmol) was dissolved in dichloromethane (1 mL) and 1,2-dichloromethane (0.25 mL) under a nitrogen atmosphere. The reaction mixture was then added slowly at 0°C to 1.9M triethyl aluminum in toluene (0.315 mL, 0.6 mmol). After stirring for 30 minutes at room temperature, to the reaction mixture was added slowly a solution of 8-oxa-bicyclo[5.1.0]octane (68 mg, 0.6 mmol) in dichloromethane (16 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 13 days and then partitioned with 1N NaOH and DCM. The organic layer was dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (2% methanol/DCM) to yield the title compound as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.05-6.88 (4H, m), 4.69 (s, 2H), 3.44-3.31 (2H, m), 2.96-2.88 (1H, m), 2.73-2.69 (1H, m), 2.56-2.53 (1H, m), 2.42-2.17 (3H, m), 2.11-2.02 (1H, m), 1.94-1.87 (1H, m), 1.78 (1H, d), 1.72-1.19 (11H, m)

MS (ES^+) *m/z* 362.3 $(M + H)^+$.

Example 11

(*R*)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*R*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #556



(*R*)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (1.5 g, 3.736 mmol) was dissolved in N, N-dimethylformamide (10.0 mL). To the reaction mixture was then added at 0°C sodium hydride (60% in mineral oil, 0.195 g, 4.856 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0°C for 40 minutes and then warmed to room temperature. To the reaction mixture was then added (S)-epichlorhydrin (0.87 mL, 11.208 mmol). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (1.5% methanol / dichloromethane) to yield the title compound as a foam.

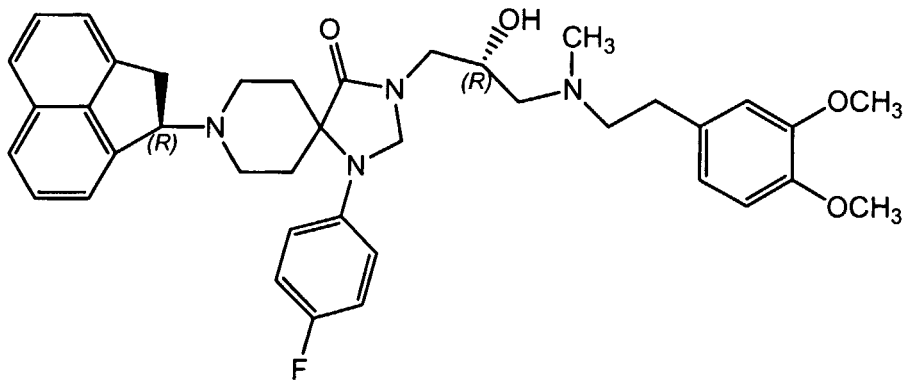
^{1}H NMR (300 MHz, $CDCl_3$) δ7.70-7.65 (1H, m), 7.60 (1H, d, J = 8.2 Hz), 7.54-7.49 (2H, m), 7.44 (1H, t), 7.26 (1H, d), 7.05-6.93 (4H, m), 4.95 (1H, dd, J = 3.4 and 7.8 Hz), 4.77-4.74 (1H, m), 4.66-4.64 (1H, m), 4.0 (1H, d, J = 12.5 Hz), 3.56-3.32 (2H, m), 3.21-3.03 (4H, m), 2.83-2.80 (2H, m), 2.59-2.55 (1H, m), 2.46-2.30 (2H, m), 2.27-2.21 (1H, m), 1.77-1.60 (2H, m)

MS (ES^+) *m/z* 458.3 $(M + H)^+$.

Example 12

(R)-8-Acenaphthen-1-yl-3-(3-{[2-(3,4-dimethoxy-phenyl)-ethyl]-methyl-amino}-(R)-2-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #339



8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5] decan-4-one (1.5 g, 3.28 mmol), [2-(3,4-dimethoxy-phenyl)-ethyl]-methyl-amine hydrochloride (2.3 g, 9.92 mmol) and *N*, *N*-diisopropylethylamine (5 mL, 28.7 mmol) were dissolved in ethanol (40 mL). The reaction mixture was heated at 80°C for 18 hours, then cooled to room temperature and the solvent evaporated *in vacuo* to yield an oil. The oil was partitioned with water and ethyl acetate. The organic layer was dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (2% [methanol in ammonia 2.0M] /dichloromethane) to yield the title compound as a foam.

Chiral resolution: Diastereoisomers were separated using a CHIRALCEL OD-H column with methanol as mobile phase and generated the two pure diastereoisomers R, R and R, S.

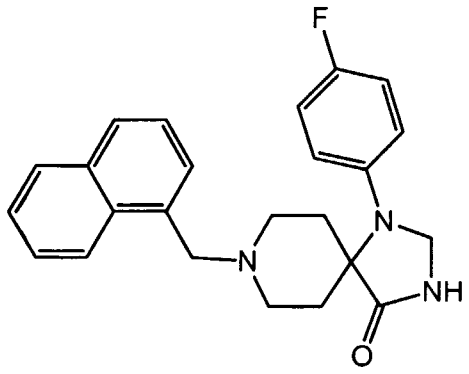
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (1H, m), 7.60 (1H, d, J = 8.2 Hz), 7.54-7.50 (2H, m), 7.44 (1H, t), 7.27-7.25 (1H, m), 7.04-6.92 (4H, m), 6.77-6.64 (3H, m), 4.97-4.94 (1H, m), 4.79-4.71 (2H, m), 3.82 (3H, s), 3.81 (3H, s), 3.58-3.51 (3H, m), 3.38-3.02 (5H, m), 2.84-2.80 (1H, m), 2.77-2.53 (4H, m), 2.49-2.26 (7H, m), 1.76-1.59 (2H, m)

MS (ES^+) *m/z* 653.4 $(M + H)^+$.

Example 13

1-(4-Fluoro-phenyl)-8-naphthalen-1-ylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #507



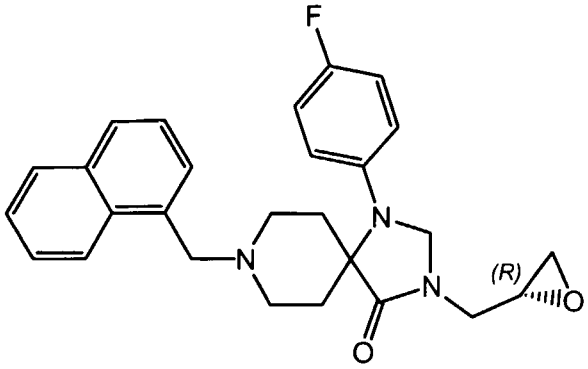
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (1.0g, 4.01 mmol) and naphthalene-1-carbaldehyde (0.75g, 4.81 mmol) were dissolved in dry tetrahydrofuran (60 mL). To the reaction mixture was then added at 0°C sodium triacetoxyborohydride (1.27g, 6.01 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (3% methanol/dichloromethane) to yield the title compound as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ8.39-8.36 (1H, m), 7.87-7.75 (2H, m), 7.56-7.37 (4H, m), 6.99-6.85 (4H, m), 4.67 (2H, s), 3.97 (2H, s), 2.91-2.83 (4H, m), 2.42-2.31 (2H, m), 1.75-1.71 (2H, m)

MS (ES^+) *m/z* 390.1 $(M + H)^+$.

Example 14

1-(4-Fluoro-phenyl)-8-naphthalen-1-ylmethyl-(R)-3-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #514



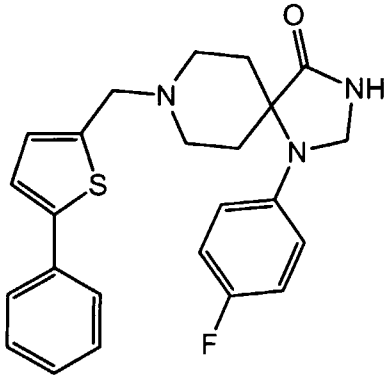
(*R*)-1-(4-Fluoro-phenyl)-8-naphthalen-1-ylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.218g, 0.559 mmol) was dissolved in N, N-dimethylformamide (2.2 mL). To the reaction mixture was then added at 0°C sodium hydride (60% in mineral oil, 30 mg, 0.727 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0°C for 40 minutes. To the reaction mixture was then added (*S*)-epichlorhydrin (0.13 mL, 1.679 mmol) at 0°C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (2% methanol/dichloromethane) to yield the title compound as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ8.38-8.35 (1H, m), 7.87-7.75 (2H, m), 7.56-7.37 (4H, m), 6.99-6.86 (4H, m), 4.78-4.65 (2H, m), 4.08-3.97 (3H, m), 3.21-3.12 (2H, m), 2.95-2.82 (5H, m), 2.61-2.59 (1H, m), 2.40-2.30 (2H, m), 1.72-1.59 (2H, m)

MS (ES^+) *m/z* 446.3 $(M + H)^+$.

Example 15

1-(4-Fluoro-phenyl)-8-(5-phenyl-thien-2-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #546



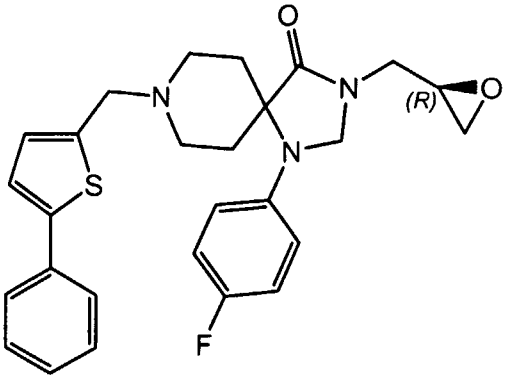
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.15g, 0.601 mmol) and 5-phenyl-thienyl-2-carbaldehyde (0.136g, 0.722 mmol) were dissolved in dry tetrahydrofuran (12 mL). To the reaction mixture was then added at 0°C sodium triacetoxyborohydride (0.192 g, 0.902 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was partitioned with 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (2% methanol/dichloromethane) to yield the title compound as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.59-7.56 (2H, m), 7.38-7.33 (2H, m), 7.27-7.22 (1H, m), 7.18-7.13 (1H, m), 7.05-6.92 (4H, m), 6.87 (1H, d, J = 3.6 Hz), 6.26 (1H, br s), 4.67 (2H, s), 3.75 (2H, s), 2.87-2.78 (4H, m), 2.40-2.30 (2H, m), 1.76 (2H, d, J = 14.1 Hz)

MS (ES^+) *m/z* 422.1 $(M + H)^+$.

Example 16

(*R*)-1-(4-Fluoro-phenyl)-3-oxiranylmethyl-8-(5-phenyl-thien-2-yl-methyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #541



1-(4-Fluoro-phenyl)-8-(5-phenyl-thien-2-yl-methyl)-1,3,8-triaza spiro[4.5]decan-4-one (0.105g, 0.249 mmol) was dissolved in N, N-dimethylformamide (2.5 mL). To the reaction mixture was then added at 0°C sodium hydride (60% in mineral oil, 13 mg, 0.323 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0°C for 40 minutes. To the reaction mixture was then added (*S*)-epichlorhydrin (0.058 mL, 0.747 mmol) at 0°C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (2% methanol/dichloromethane) to yield the title compound as a solid.

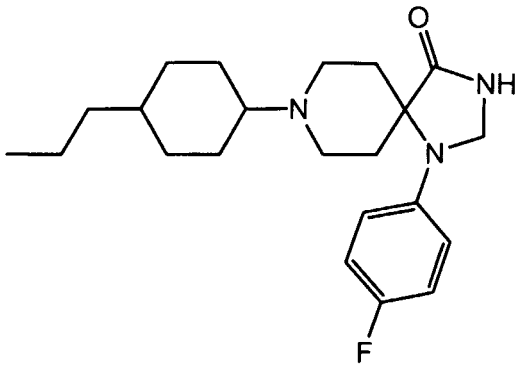
^{1}H NMR (300 MHz, $CDCl_3$) δ7.59-7.55 (2H, m), 7.38-7.33 (2H, m), 7.27-7.22 (1H, m), 7.14 (1H, d, J = 3.6 Hz), 7.05-6.92 (4H, m), 6.87 (1H, d, J = 3.5 Hz), 4.77 (1H, d, J = 4.8 Hz), 4.66 (1H, d, J = 4.8 Hz), 4.06-3.99 (1H, m), 3.76 (2H, s), 3.20-3.13 (2H, m), 2.95-2.82 (3H, m), 2.60-2.58 (1H, m), 2.38-2.30 (2H, m), 1.75-1.67 (2H, m)

MS (ES^+) *m/z* 478.2 $(M + H)^+$.

Example 17

1-(4-Fluoro-phenyl)-8-(4-propyl-cyclohexyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #504



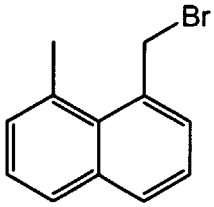
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.25 g, 1.00 mmol) was dissolved in dry toluene (10 mL). To the reaction mixture was then added 4-propyl-cyclohexanone (0.14g, 1.00 mmol), powder molecular sieve 4A (0.5g) and the reaction mixture was refluxing for 18 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered through Celite. The Celite cake was washed with dry dichloromethane and the combined filtrate evaporated *in vacuo* to dryness. The residue was dissolved in dry tetrahydrofuran (4 mL) and dry methanol (0.5 mL). To the solution was then added sodium cyanoborohydride (21 mg), the pH of the solution was adjusted to pH 4 with a few drops of glacial acetic acid and the reaction mixture was stirred for 48 hours at room temperature under nitrogen atmosphere. The reaction mixture was partitioned with 1N NaOH and ethyl acetate. The organic layer was dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (gradient 2-4% methanol/dichloromethane) to yield the title compound.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.02-6.93 (4H, m), 6.54 (1H, br d, J = 9.1 Hz), 4.67 (2H, s), 3.05-2.70 (4H, m), 2.38-2.15 (3H, m), 1.9-1.11 (15H, m), 0.94-0.84 (3H, m)

MS (ES^+) *m/z* 374.0 $(M + H)^+$.

Example 18

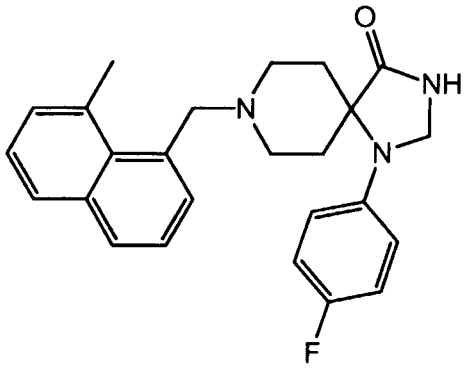
1-Bromomethyl-8-methyl-naphthalene



1,8-Dimethyl-naphthalene (1.30 g, 8.32 mmol) was dissolved in dry carbon tetrachloride (80 mL). To the reaction mixture was added *N*-bromosuccinimide (1.39 g, 7.82 mmol), dibenzoyl peroxide (6 mg, catalyst) and the reaction mixture was refluxing for 6 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature, a precipitate formed on cooling and the precipitate was separated by filtration. The filtrate was evaporated *in vacuo* to yield the title compound as a solid which was used in further steps without additional purification.

Example 19

1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]-decan-4-one Compound #547



1-Bromomethyl-8-methyl-naphthalene (1.72 g, 7.31 mmol) and 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (1.29 g, 5.17 mmol) were dissolved in N, N-dimethylformamide (50 mL). Potassium carbonate (2.4 g, 15.52 mmol) and potassium iodide (0.02 g) were added and the reaction mixture was stirred at 30°C under nitrogen atmosphere for 18 hours. The reaction mixture was partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent

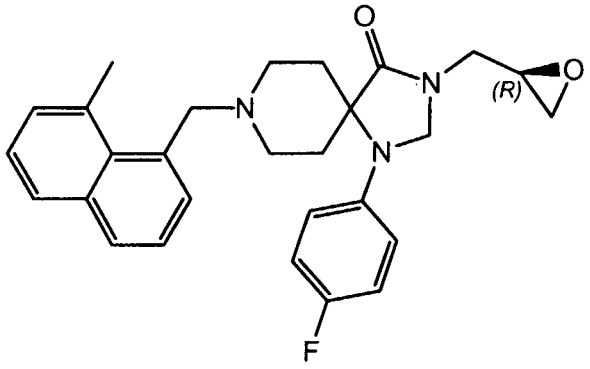
evaporated *in vacuo* to yield a crude solid. The crude solid was recrystallized from diethyl ether to yield the title compound as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.76 (1H, m), 7.72-7.69 (1H, m), 7.39-7.30 (4H, m), 6.98-6.92 (2H, m), 6.87-6.82 (2H, m), 6.24 (1H, br s), 4.66 (2H, s), 4.01 (2H, s), 3.12 (3H, s), 2.86-2.78 (4H, m), 2.33-2.23 (2H, m), 1.72 (2H, d, J = 14.1 Hz)

MS (ES^+) m/z 404.2 $(M + H)^+$.

Example 20

1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*R*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #553



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]-decan-4-one (0.91 g, 2.25 mmol) was dissolved in N, N-dimethylformamide (10.5 mL). To the reaction mixture was then added at 0°C sodium hydride (60% in mineral oil, 117 mg, 2.93 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0°C for one hour, then warmed to room temperature. To the reaction mixture was then added (*S*)-epichlorhydrin (0.53 mL, 6.76 mmol). The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (2.5% methanol/dichloromethane) to yield the title compound as a foam.

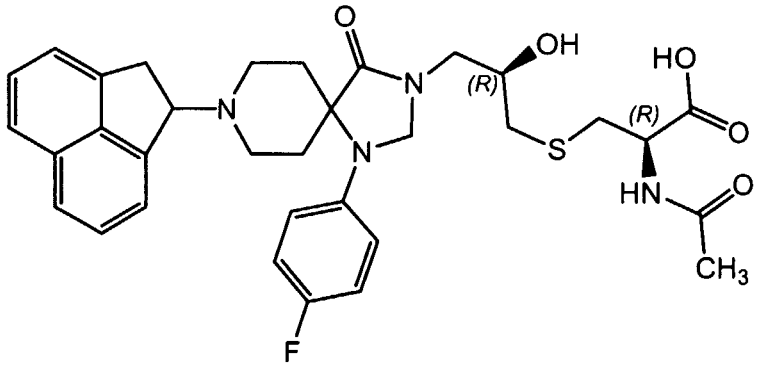
^{1}H NMR (300 MHz, $CDCl_3$) δ7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.39-7.30 (4H, m), 6.99-6.92 (2H, m), 6.88-6.83 (2H, m), 4.76 (1H, d, J = 4.8 Hz),

4.64 (1H, d, J = 4.8 Hz), 4.0 (2H, s), 3.21-3.11 (6H, m), 2.86-2.78 (5H, m), 2.60-2.58 (1H, m), 2.30-2.22 (2H, m), 1.70-1.62 (2H, m)

MS (ES^+) m/z 460.2 $(M + H)^+$.

Example 21

3-{3-[8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-(R)-hydroxy-propylsulfanyl}-2-acetylamino-(R)-propionic acid Compound #100

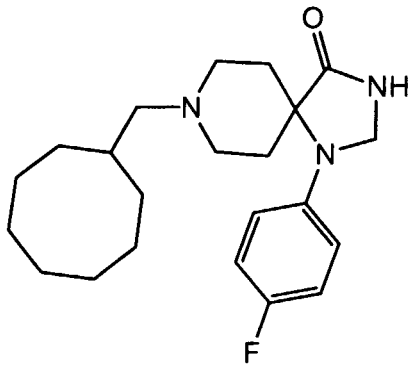


8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*R*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.022 g, 0.048 mmol) and *N*-acetyl-L-cysteine (0.03 g, 0.184 mmol) were dissolved in ethanol (1 mL). The reaction mixture was heated at 80°C for 18 hours, then cooled to room temperature and the solvent evaporated *in vacuo* to yield an oil. The oil was partitioned with water and ethyl acetate. The organic layer was dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via preparative TLC plate (10% methanol/dichloromethane) to yield the title compound as an oil.

Example 22

8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compounds #582



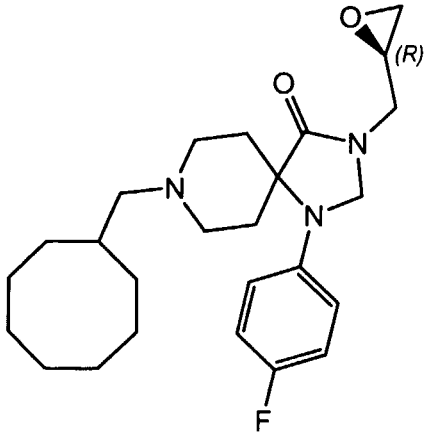
Cyclooctanecarbaldehyde (0.676g, 4.8 mmol) synthesized according to the procedure described in Kawamoto, H. et.al. *Tetrahedron* **2001**, *57*, 981-986 was reacted with 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (1 g, 4 mmol) in tetrahydrofuran (anhydrous, 100 mL), with the addition of sodium triacetoxyborohydride (1.2g, 6 mmol) at 0°C. The reaction was then stirred overnight at room temperature. The organic layer was partitioned with 1N sodium hydroxide, water and brine. The organic layer was dried with sodium sulfate and filtered to yield a clear residue. Purification of the residue by flash chromatography yielded the title compound as a white powder.

MS (electrospray) = 374.1 (MH+)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1-1.9 (m, 15H), 2.1 (d, 2H), 2.2-2.4 (m, 2H), 2.7 (d, 4H), 3.3 (d, 2H), 4.7 (s, 2H), 6.4 (s, 1H), 6.8-7.0 (m, 4H).

Example 23

8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-(R)-3-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #540



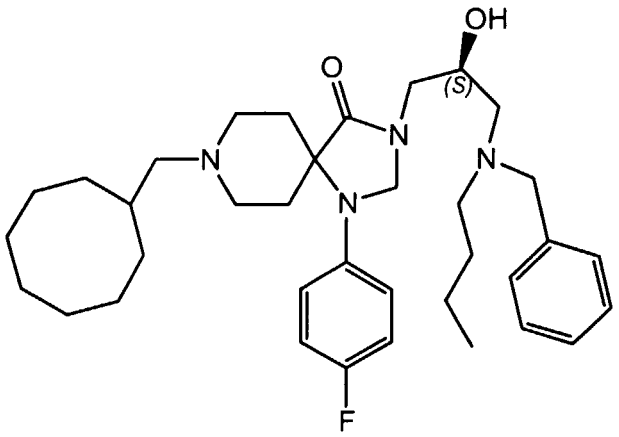
8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (4, 3 g, 8 mmol) was dissolved with NMP(150 mL) and stirred at 0°C. Sodium hydride (60% dispersion in oil, 0.75 g, 18.7 mmol) was added to the reaction mixture which was then stirred an additional 30 minutes at 0°C. S-(+)-epichlorohydrin (1.88ml, 24 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was then partitioned with water and ethyl acetate. The organic was dried with sodium sulfate and filtered. The solvent was evaporated to yield the title compound as an oil.

MS (electrospray) = 430.5 (MH+)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1-1.9 (m, 17H), 2.15 (d, 2H), 2.2-2.4 (m, 2H), 2.5-2.85 (m, 4H), 3.1 (m, 2H), 4.0 (m, 1H), 4.65 (d, 1H), 4.75 (d, 1H), 6.8-7.0(m, 4H)

Example 24

3-[3-(Benzyl-butyl-amino)-2-(S)-hydroxy-propyl]-8-cyclooctylmethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #64



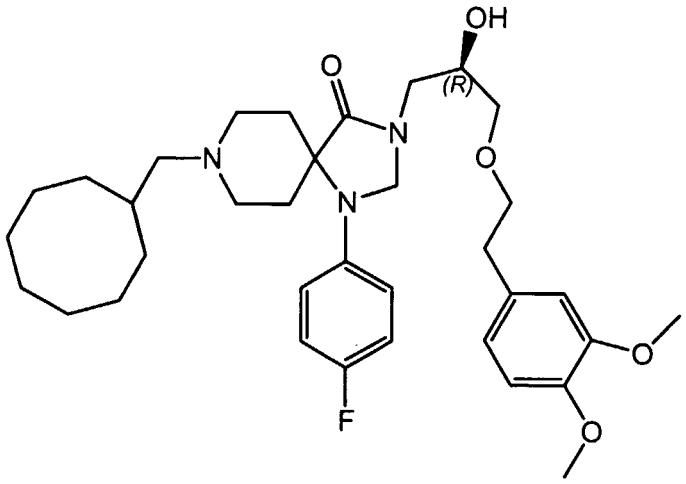
Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (3.4 g, 8 mmol) was dissolved in absolute ethanol (75 mL), mixed with N-butylbenzylamine (3.1 mL, 17.6 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by column chromatography (5% MeOH/CH_2Cl_2) to yield the free base as an oil. The oil (2.2g, 3.7 mmol) was dissolved in diethyl ether (10mL) and reacted with HCl (11mL, [1M in diethylether]) at 0°C. He resulting crystals were collected by filtration and recrystallized with eethanol to yield 1g the title compound white powder.

MS (electrospray) = 593.5 (MH+), 592.6

^{1}H NMR (300 MHz, CD_3OD) δ 1.1 (m, 3H), 1.3-1.9 (m, 15H), 2.1 (m, 2H), 2.4 (m, 2H), 2.9-3.6 (m, 14H), 3.65-3.8 (m, 2H), 4.2 (m, 1H), 4.3-4.3 (m, 3H), 4.8 (m, 2H), 7.0-7.2 (m, 4H), 7.4-7.7 (m, 5H)

Example 25

8-Cyclooctylmethyl-3-{3-[2-(3,4-dimethoxy-phenyl)-ethoxy]-2-(R)-hydroxy-propyl}-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #105



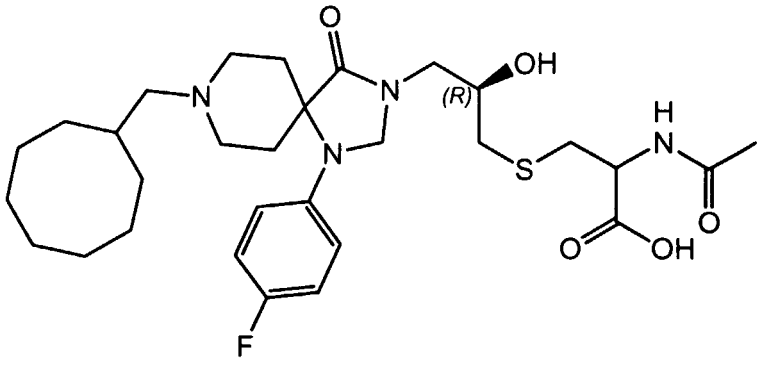
3, 4-Dimethoxyphenethylalcohol was dissolved in NMP (2 mL) and stirred for 30 min. NaH (60% dipersion in oil) was added and the mixture was stirred for thirty minutes. 8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.2 g, 0.46 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was partitioned with saturated $NaHCO_3$ solution and ethyl acetate. The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated *in vacuo* to yield crude product. Purification by reverse phase chromatography (AcCN/water) yielded the title compound as a trifluoroacetate salt as a solid.

MS (electrospray) = 612.1 (MH+), 522.0, 402.2

^1H NMR (300 MHz, CD_3OD) δ 1.3-1.8 (m, 14H), 2.0-2.1 (m, 4H), 2.2-2.4 (m, 2H), 2.8 (t, 2H), 3.0 (d, 2H), 3.35-3.8 (m, 13H), 3.9 (m, 4H), 4.7 (m, 2H), 6.8 (m, 3H), 7.1 (m, 4H)

Example 26

2-Acetylamino-3-{3-[8-cyclooctylmethyl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-(R)-hydroxy-propylsulfanyl}-propionic acid Compound #100

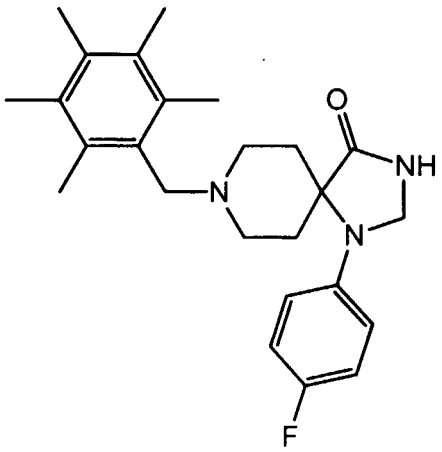


1-(4fluorophenyl)-3R-oxarinyl-methyl-8-cyclooctylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.06 g, 0.14 mmol) was dissolved in absolute ethanol (1 mL), mixed with N-acetylcysteine (68 mg, 0.42 mmol) and heated to 70°C overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (AcCN/water) to yield the title compounds as a trifluoroacetate salt as a solid.

MS (electrospray) = 593.8 (MH+).

Example 27

1-(4-Fluoro-phenyl)-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #583



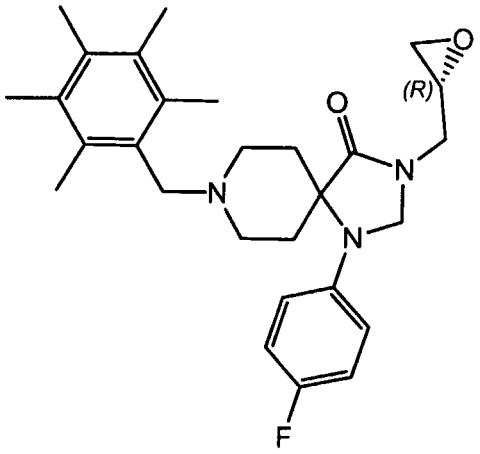
Pentamethylbenzaldehyde (4 g, 23 mmol, commercially available) was reacted with 1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (5.5 g, 20 mmol) in tetrahydrofuran (anhydrous, 250 mL), with addition of sodium triacetoxyborohydride (8.2 g, 42 mmol) at 0°C. The reaction was then stirred overnight at room temperature. The organic layer was partitioned with 1N sodium hydroxide, water and brine. The organic layer was dried with sodium sulfate and filtered to yield the title compound as a white powder.

MS (electrospray) = 410.5 (MH+), 250.0

^{1}H NMR (300 MHz, DMSO-d_6) δ 1.6 (d, 2H), 2.2-2.3 (m, 17 H), 2.6-2.8 (m, 4H), 3.55 (s, 2H), 4.5 (s, 2H), 6.8 (m, 2H), 7.1 (t, 2H), 8.65 (s, 1H.

Example 28

1-(4-Fluoro-phenyl)-3R-oxiranylmethyl-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #584

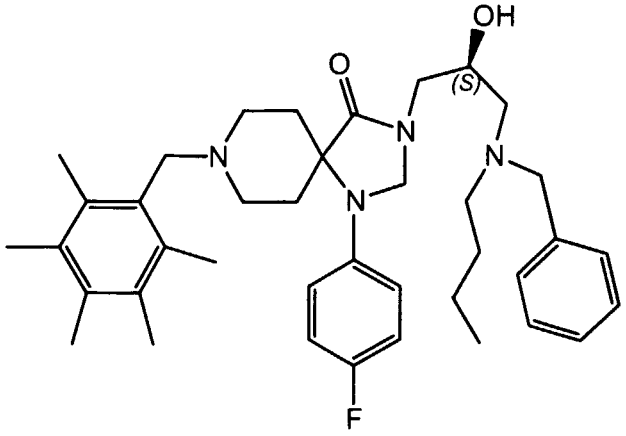


1-(4-Fluoro-phenyl)-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.6 g, 1.46 mmol) was dissolved with NMP (5 mL) and stirred at room temperature. Sodium hydride (60% dispersion in oil, 0.11 g, 1.6 mmol) was added and the mixture stirred an additional 30 minutes. S-(+)-epichlorohydrin (0.3 ml, 3.2 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was then partitioned with water and ethyl acetate. The organic was dried with sodium sulfate and filtered. The solvent was evaporated to yield the title compounds as an oil.

MS (electrospray) = 466.1 (MH+)

Example 29

3-[3-(Benzyl-butyl-amino)-2-(S)-hydroxy-propyl]-1-(4-fluoro-phenyl)-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #280



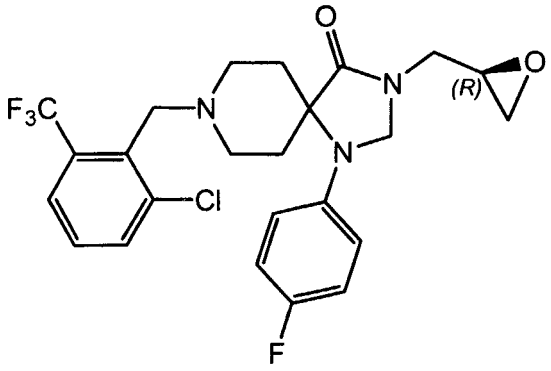
1-(4-Fluoro-phenyl)-3R-oxiranylmethyl-8-pentamethylphenylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.1 g, 0.21 mmol) was dissolved in absolute ethanol (75 mL), mixed with N-butylbenzylamine (0.1 mL, 0.6 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (AcCN/water) to yield the title compound as an oil.

MS (electrospray) = 629.2 (MH+), 468.9, 315.3, 311.9, 161.1

^{1}H NMR (300 MHz, CD_3OD) δ 1.0 (m, 3H), 1.3 (m, 2 H), 1.8 (m, 2H), 1.9 (m, 2H), 2.25 (d, 9H), 2.3(s, 6H), 3.2 (m, 3H), 3.4 (m, 4H), 3.9 (m, 3H), 4.15 (m, 1H), 4.4 (m, 4H), 4.8 (m, 2H), 7.0 (m, 3H), 7.5 (m, 9H).

Example 30

8-(2-Chloro-6-trifluoromethyl-benzyl)-1-(4-fluoro-phenyl)-3R-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #578

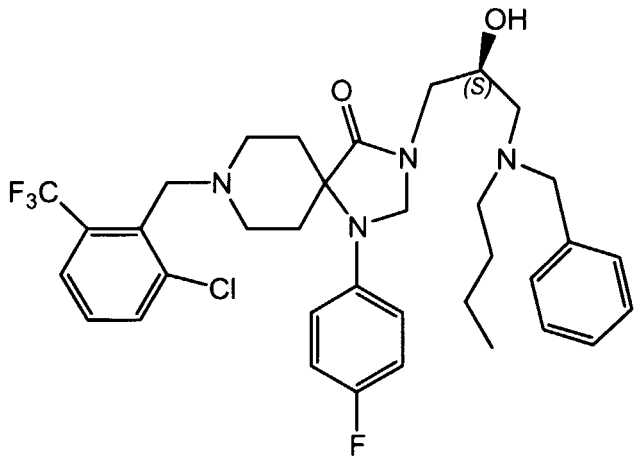


8-(2-Chloro-6-trifluoromethyl-benzyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.3 g, 0.68 mmol) was dissolved with NMP (20 mL) and stirred at room temperature. Sodium hydride (60% dispersion in oil, 0.066 g, 0.95 mmol) was added and the mixture was stirred an additional 30 minutes. S-(+)-epichlorohydrin (0.14 ml, 1.5 mmol) was added and the reaction was stirred overnight at room temperature. The reaction was then partitioned with water and ethyl acetate. The organic was dried with sodium sulfate and filtered. The solvent was evaporated to yield the title compound as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.6 (m, 2H), 2.3 (m, 2 H), 2.7 (m, 2H), 2.9 (bt, 2H), 3.1 (m, 1H), 3.8 (s, 2H), 4.0 (d, 1H), 4.6 (d, 1H), 4.8 (d, 2H), 6.8 (m, 2H), 6.95 (m, 2H), 7.2 (t, 1H), 7.6 (t, 2H).

Example 31

3-[3-(Benzyl-butyl-amino)-2-(S)-hydroxy-propyl]-8-(2-chloro-6-trifluoromethyl-benzyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #456)

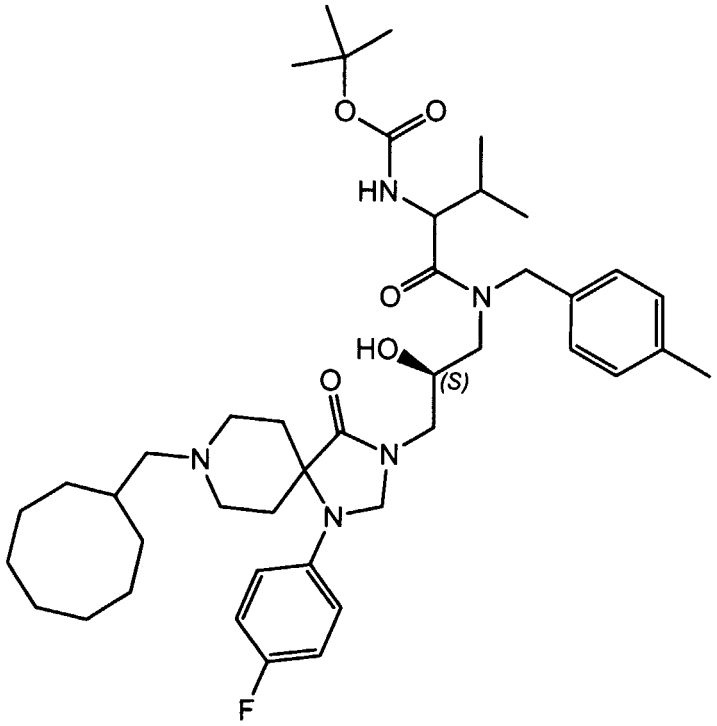


8-(2-Chloro-6-trifluoromethyl-benzyl)-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.05 g, 0.1 mmol) was dissolved in absolute ethanol (0.5 mL), mixed with N-butylbenzylamine (0.05 mL, 0.4 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse column chromatography (AcCN/water) to yield the title compound as an oil.

MS (electrospray) = 661.0 (MH+), 571.1, 331.4

Example 32

{1-[{3-[8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-(S)-hydroxy-propyl}-(4-methyl-benzyl)-carbamoyl]-2-methyl-propyl}-carbamic acid tert-butyl ester Compound #79

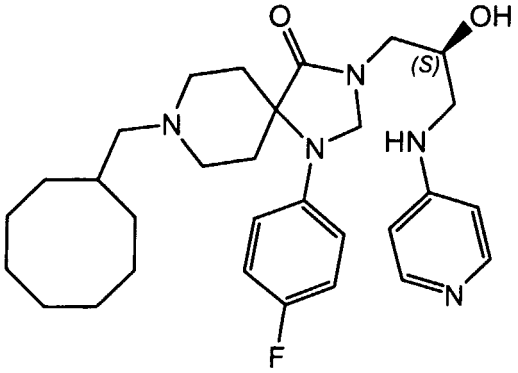


8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-[2-hydroxy-3-(4-methyl-benzylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one (0.05 g, 0.091 mmol) was dissolved in DMF (1 mL), mixed with BocD-Valine (0.02 g, 0.091mmol), HBTU (0.035 g, 0.09 mmol) and diisopropylethylamine (0.1mL) and stirred overnight at room temperature. The reaction mixture was partitioned with saturated $NaHCO_3$ and ethyl acetate. The organic layer dried with $MgSO_4$, filtered and the solvent evaporated *in vacuo* to yield the title compound as an oil.

MS (electrospray) = 751.5 (MH+), 749.8, 373.6, 372.8, 203.1, 171.1

Example 33

8-Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-[2-(S)-hydroxy-3-(pyridin-4-ylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #36

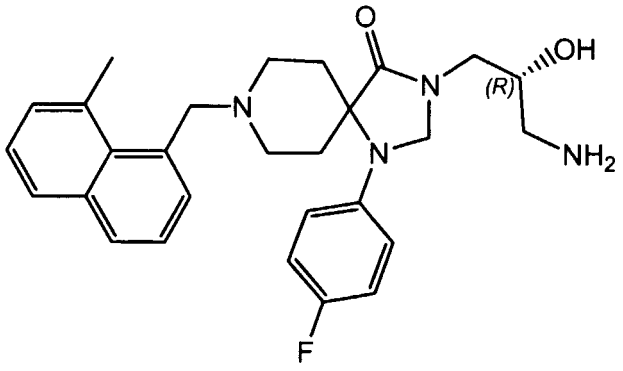


Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.5 g, 1.16 mmol) was dissolved in absolute ethanol (1 mL), mixed with 4-Aminopyridine (0.5 mL, 5.3 mmol) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse phase column chromatography (Acetonitrile/water) to yield the title compound as an oil.

^{1}H NMR (300 MHz, CD_3OD) δ 1.35 (m, 2H), 1.5-1.7 (m, 13 H), 1.9 (s, 9H), 1.95 (m, 1H), 2.4 (m, 2H), 3.1 (d, 2H), 3.2 (m, 2H), 3.4 (m, 2H), 3.55 (d, 2H), 4.0 (m, 1H), 4.15 (m, 1H), 4.3 (m, 1H), 6.8 (d, 2H), 7.1(m, 4H), 8.1(d, 2H).

Example 34

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound#438



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.06 g, 0.13 mmol) was

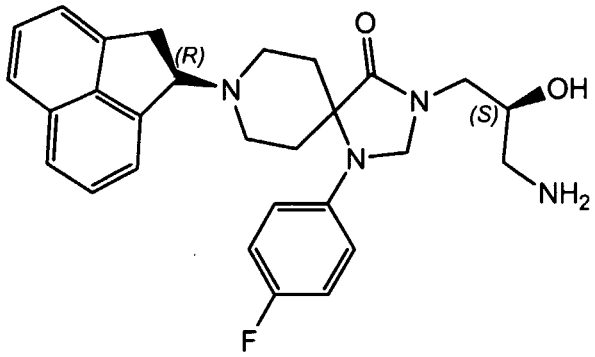
dissolved in ethyl alcohol (2 mL) and methyl alcohol (0.4 mL). To the solution was then added concentrated ammonium hydroxide (1 mL) and the reaction mixture was stirred at 40°C for two hours in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ7.77-7.75 (1H, m), 7.71-7.68 (1H, m), 7.37-7.30 (4H, m), 6.97-6.91 (2H, m), 6.87-6.83 (2H, m), 4.74 (2H, s), 4.0 (2H, s), 3.79-3.74 (1H, m), 3.57-3.52 (1H, m), 3.41-3.36 (1H, m), 3.11 (3H, s), 2.91-2.74 (4H, m), 2.66-2.61 (1H, m), 2.30-2.23 (2H, m), 1.66 (2H, d, J = 13.7 Hz)

MS (ES^+) *m/z* 477.1 $(M + H)^+$.

Example 35

(R)-8-Acenaphthen-1-yl-3-(3-amino-2-hydroxy-(S)-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #424



(*R*)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*R*) oxiranylmethyl-1,3,8-triaza-spiro[4.5] decan-4-one (0.514 g, 1.123 mmol) was dissolved in ethyl alcohol (16 mL). To the solution was then added concentrated ammonium hydroxide (8 mL) and the reaction mixture was stirred at 40°C for two hours and a half in a pressure flask. The solvent was then evaporated *in vacuo* to yield the title compound as a foam.

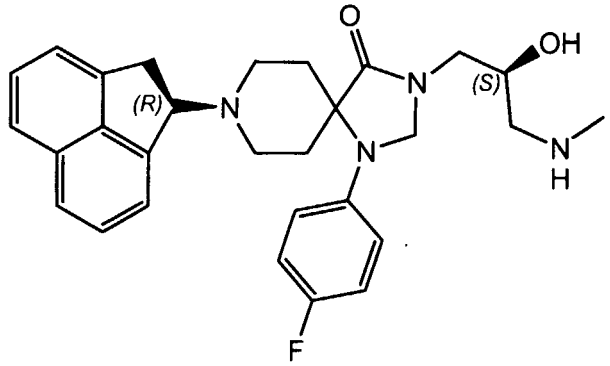
^{1}H NMR (400 MHz, $CDCl_3$) δ7.68-7.65 (1H, m), 7.60 (1H, d, J = 8.2 Hz), 7.52-7.49 (2H, m), 7.43 (1H, t), 7.26 (1H, d), 7.03-6.94 (4H, m), 4.97-4.94 (1H, m), 4.76-4.72 (2H, m), 3.74 (1H, br s), 3.55-3.48 (2H, m), 3.38-3.32 (2H, m),

3.16-3.03 (2H, m), 2.88-2.82 (2H, m), 2.59 (1H, br s), 2.44-2.41 (2H, m), 2.31-2.24 (1H, m), 1.76-1.62 (2H, m)

MS (ES^+) *m/z* 475.2 $(M + H)^+$.

Example 36

(R) 8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(2-hydroxy-3-methylamino-(S)-propyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #437



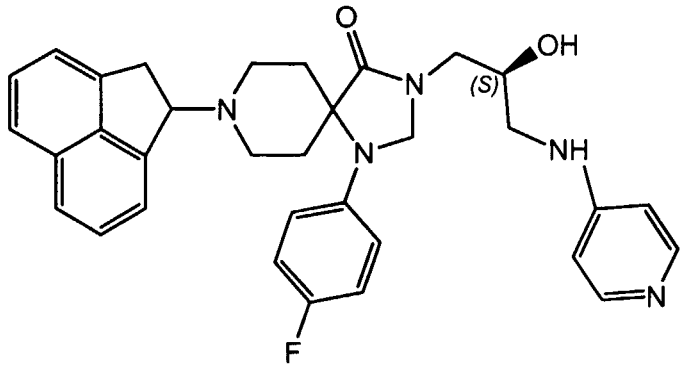
(*R*)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*R*) oxiranylmethyl-1,3,8-triaza-spiro[4.5] decan-4-one (0.045 g, 0.098 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added a solution of 2.0M methylamine in THF (1 mL) and the reaction mixture was stirred at 40°C for two hours and a half in a pressure flask. The solvent was then evaporated *in vacuo* to yield the title compound as a foam.

^1H NMR (400 MHz, $CDCl_3$) δ7.68-7.64 (1H, m), 7.59 (1H, d, J = 8.2 Hz), 7.53-7.49 (2H, m), 7.45 (1H, t), 7.26-7.24 (1H, m), 7.03-6.94 (4H, m), 4.96-4.93 (1H, m), 4.78-4.73 (2H, m), 3.86-3.83 (1H, m), 3.55-3.47 (2H, m), 3.37-3.30 (2H, m), 3.16-2.99 (2H, m), 2.87-2.79 (2H, m), 2.70-2.66 (1H, m), 2.52-2.23 (6H, m), 1.75-1.61 (2H, m)

MS (ES^+) *m/z* 489.3 $(M + H)^+$.

Example 37

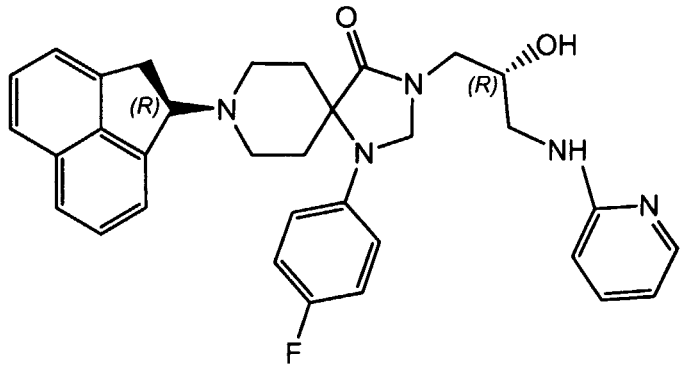
8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-hydroxy-3-(pyridin-4-ylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #327



8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*R*) oxiranylmethyl-1,3,8-triaza-spiro[4.5] decan-4-one (0.100 g, 0.21 mmol) was dissolved in absolute ethyl alcohol (0.5 mL), mixed with 4-aminopyridine (0.2 mL) and heated at reflux overnight. The solvent was evaporated and the resulting residue was purified by reverse phase chromatography (MeCN/water) to yield the title compound as an oil.

Example 38

(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-hydroxy-3-(pyridin-2-ylamino)-(R)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one Compound #421



Sodium amide (0.0085g, 0.21 mmol) and 2-aminopyridine (0.0165g, 0.17 mmol) were suspended in toluene (0.25 mL) and benzene (0.15 mL). To the reaction mixture was then added (*R*)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*S*) oxiranylmethyl-1,3,8-triaza-spiro [4.5]decan -4-one (0.100 g, 0.21 mmol). The mixture was refluxed overnight under nitrogen, cooled down to

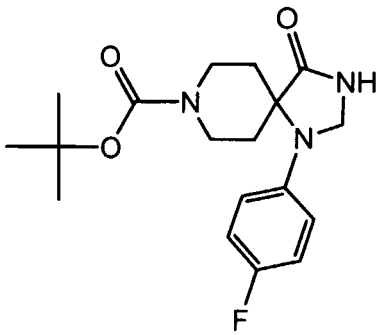
room temperature and partitioned with brine and dichloromethane. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (3.25% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.98-7.96 (1H, m), 7.69-7.65 (1H, m), 7.60 (1H, d, J = 8.2 Hz), 7.53-7.51 (2H, m), 7.47-7.40 (1H, m), 7.28-7.26 (1H, m), 7.03-6.92 (4H, m), 6.66-6.47 (3H, m), 5.08-5.04 (1H, m), 4.98-4.94 (1H, m), 4.79-4.73 (2H, m), 4.0-3.94 (1H, m), 3.72-3.61 (2H, m), 3.57-3.49 (1H, m), 3.40-3.28 (2H, m), 3.14-3.02 (2H, m), 2.85-2.81 (1H, m), 2.44-2.26 (3H, m), 1.74-1.25 (2H, m)

MS (ES^+) *m/z* 552.3 $(M + H)^+$.

Example 39

1-(4-Fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester Compound #535



Di-*tert*-butyl dicarbonate (2.2 g, 10.0 mmol) and 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (2.5 g, 10.0 mmol) were dissolved in dioxane (50 mL) and water (100 mL). Sodium hydrogeno carbonate (1.7 g, 20 mmol) was then added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours. The reaction mixture was concentrated *in vacuo* and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a solid. Recrystallization from hot ethyl acetate yielded the title compound as a white solid.

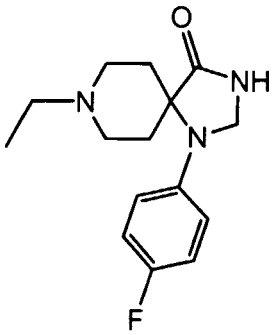
^{1}H NMR (300 MHz, $CDCl_3$) δ8.25 (1H, br s), 7.0-6.95 (2H, m), 6.82-6.77 (2H, m), 4.71 (2H, s), 4.08-3.8 (2H, m), 3.65-3.40 (2H, m), 2.35-2.15 (2H, m), 1.8-1.65 (2H, m), 1.48 (9H, s)

MS (ES^+) *m/z* 372.1 $(MNa)^+$.

Example 40

8-Ethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #536



2-iodoethane (0.47 g, 3.0 mmol) and 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.6 g, 2.4 mmol) were dissolved in acetonitrile (15 mL). Potassium carbonate (0.66 g, 4.8 mmol) was then added and the reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours. The reaction mixture was partitioned with water and diethyl ether. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (30-50% ethyl acetate / hexane) to yield the title compound as an oil.

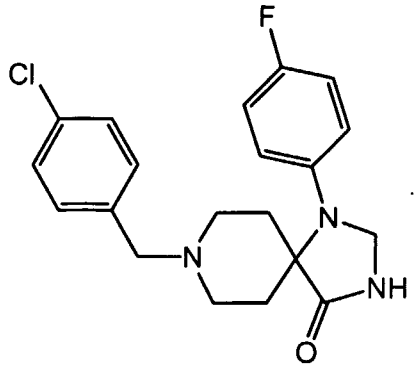
^{1}H NMR (300 MHz, $CDCl_3$) δ7.03-6.93 (4H, m), 6.46 (1H, br s), 4.67 (2H, s), 2.82-2.69 (4H, m), 2.48 (2H, q), 2.31-2.21 (2H, m), 1.81-1.76 (2H, m), 1.08 (3H, t)

MS (ES^+) *m/z* 278.2 $(M + H)^+$.

Example 41

8-(4-Chloro-benzyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #508



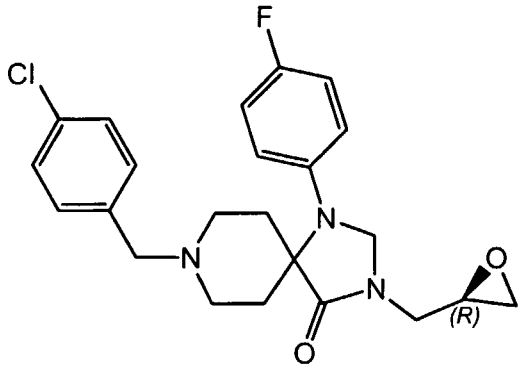
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (3.0g, 12.03 mmol) and 4-chloro-benzaldehyde (2.03g, 14.44 mmol) were dissolved in dry tetrahydrofuran (120 mL). To the reaction mixture was then added at 0°C sodium triacetoxyborohydride (3.82g, 18.05 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (3.5% methanol/dichloromethane) to yield the title compound as a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.30-7.15 (4H, m), 7.01-6.87 (4H, m), 4.63 (2H, s), 3.47 (2H, s), 2.78-2.65 (4H, m), 2.31-2.0 (2H, m), 1.73-1.68 (2H, m)

MS (ES^+) *m/z* 374.1 $(M + H)^+$.

Example 42

8-(4-Chloro-benzyl)-1-(4-fluoro-phenyl)-3-(R)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #513



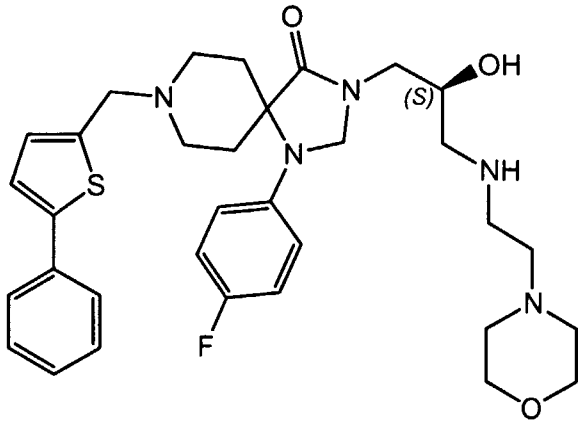
8-(4-Chloro-benzyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.220g, 0.588 mmol) was dissolved in N, N-dimethylformamide (2.2 mL). To the reaction mixture was then added at 0°C sodium hydride (60% in mineral oil, 31 mg, 0.765 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0°C for 40 minutes. To the reaction mixture was then added (*S*)-epichlorhydrin (0.14 mL, 1.765 mmol) at 0°C. The reaction mixture was stirred at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (2% methanol / dichloromethane) to yield the title compound as a foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.32-7.26 (4H, m), 7.04-6.91 (4H, m), 4.77 (1H, d, J = 4.9 Hz), 4.66 (1H, d, J = 4.9 Hz), 4.06-3.99 (1H, m), 3.52 (3H, s), 3.20-3.14 (2H, m), 2.85-2.68 (5H, m), 2.60-2.58 (1H, m), 2.33-2.23 (2H, m), 1.73-1.60 (2H, m)

MS (ES^+) *m/z* 430.2 $(M + H)^+$.

Example 43

1-(4-Fluoro-phenyl)-3-(S)-[2-hydroxy-3-(2-morpholin-4-yl-ethylamino)-propyl]-8-(5-phenyl-thien-2-yl-methyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #293



(*R*)-1-(4-Fluoro-phenyl)-3-oxiranylmethyl-8-(5-phenyl-thien-2-yl-methyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.02 g, 0.041 mmol) was dissolved in absolute ethanol (1 mL), mixed with 2-morpholin-4-yl-ethylamine (16.3 mg, 0.125 mmol) and heated under stirring at 70°C overnight. The solvent was evaporated and the resulting residue was purified via flash chromatography (9% methanol/dichloromethane) to yield the title compound as an oil.

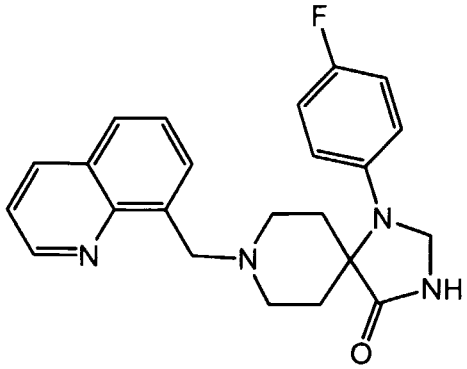
^{1}H NMR (300 MHz, $CDCl_3$) δ7.59-7.56 (2H, m), 7.38-7.33 (2H, m), 7.28-7.25 (2H, m), 7.14 (1H, d, J = 3.6 Hz), 7.04-6.91 (3H, m), 6.87 (1H, d, J = 3.5 Hz), 4.80-4.76 (2H, m), 3.86-3.69 (6H, m), 3.61-3.55 (1H, m), 3.36-3.29 (1H, m), 2.85-2.71 (7H, m), 2.58-2.32 (10H, m), 1.72 (2H, d, J = 13.7 Hz)

MS (ES^+) *m/z* 608.3 $(M + H)^+$

Example 44

1-(4-Fluoro-phenyl)-8-quinolin-8-ylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #522



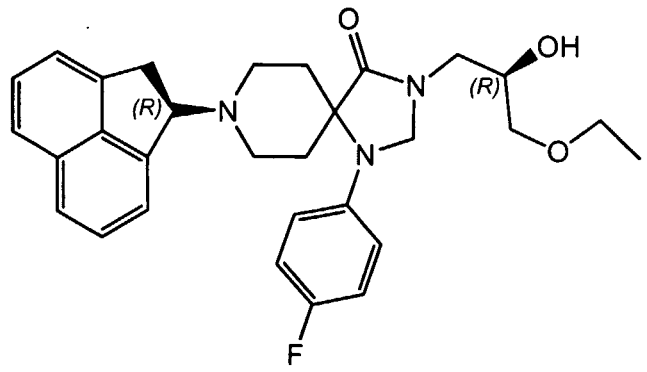
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.15g, 0.601 mmol) and quinoline-8-carbaldehyde (0.113g, 0.722 mmol) were dissolved in dry tetrahydrofuran (12 mL). To the reaction mixture was then added at 0°C sodium triacetoxyborohydride (0.192g, 0.902 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5% methanol/dichloromethane) to yield the title compound as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ8.93-8.91 (1H, m), 8.14 (1H, d, J = 8.3 Hz), 7.89 (1H, br s), 7.71 (1H, m), 7.55 (1H, t, J = 7.7 Hz), 7.41-7.38 (1H, m), 7.05-7.01 (4H, m), 6.79 (1H, br s), 4.69 (2H, s), 4.35 (2H, s), 3.01-2.90 (4H, m), 2.41 (2H, br s), 1.80 (2H, d, J = 13.8 Hz)

MS (ES^+) *m/z* 391.0 $(M + H)^+$.

Example 45

(R)-8-Acenaphthen-1-yl-3-(R)-(3-ethoxy-2-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #571



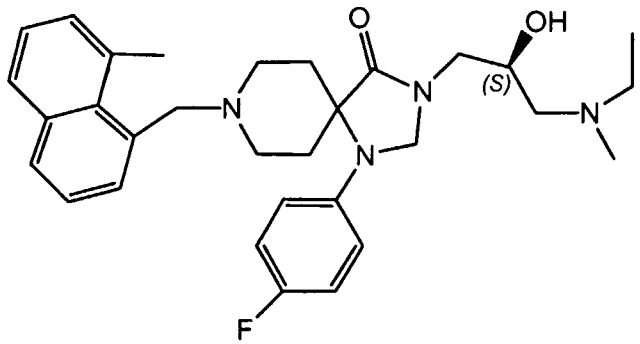
(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*R*) oxiranyl-methyl-1,3,8-triaza-spiro[4.5] decan-4-one (0.084 g, 0.183 mmol) was dissolved in ethanol (4 mL). The reaction mixture was heated at 80°C for 18 hours, then cooled to room temperature and the solvent evaporated *in vacuo* to yield an oil. The oil was partitioned with water and ethyl acetate. The organic layer was dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (4% [methanol in ammonia 2.0M] /dichloromethane) to yield the title compound as an oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.69-7.66 (1H, m), 7.61 (1H, d, J = 8.2 Hz), 7.54-7.50 (2H, m), 7.44 (1H, t), 7.27-7.25 (1H, m), 7.05-6.90 (4H, m), 4.98-4.90 (1H, m), 4.77-4.71 (2H, m), 4.03-3.98 (1H, m), 3.57-3.31 (8H, m), 3.16-3.01 (3H, m), 2.88-2.85 (1H, m), 2.43 (2H, br s), 2.32-2.24 (1H, m), 1.77-1.62 (2H, m), 1.18 (3H, t);

MS (ES^+) *m/z* 504.3 $(M + H)^+$.

Example 46

3-[3-(Ethyl-methyl-amino)-2-hydroxy-(S)-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,,3,8-triaza-spiro[4.5]decan-4-one Compound #440



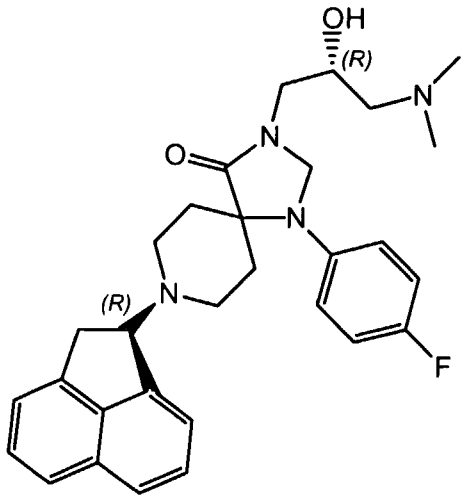
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*R*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.02 g, 0.043 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added N-methylethylamine (0.2 mL) and the reaction mixture was stirred at 40°C for 3 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ7.77-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.30 (4H, m), 6.96-6.91 (2H, m), 6.88-6.84 (2H, m), 4.82-4.75 (2H, m), 4.08-3.98 (3H, m), 3.61-3.57 (1H, m), 3.34-3.29 (1H, m), 3.11 (3H, s), 2.83-2.54 (8H, m), 2.44 (3H, s), 2.32-2.23 (2H, m), 1.68-1.63 (2H, m); 1.15 (3H, t, J = 7.2 Hz)

MS (ES^+) *m/z* 519.3 $(M + H)^+$.

Example 47

(*R*)-Acenaphthen-1-yl-3-(3-dimethylamino-2-hydroxy-(*R*)-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #423



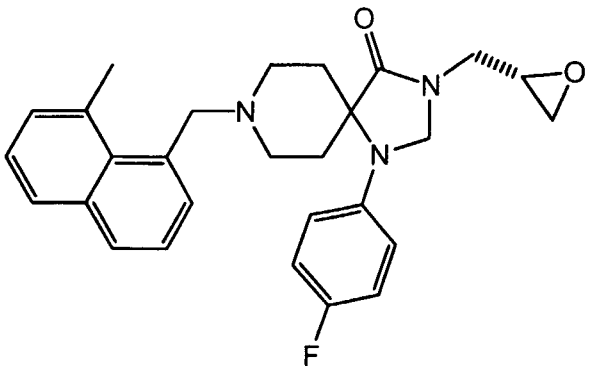
(*R*)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*S*) oxiranylmethyl-1,3,8-triaza-spiro[4.5] decan-4-one (0.057 g, 0.124 mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added a solution of 2.0M dimethylamine in THF (1 mL) and the reaction mixture was stirred at 40°C for 2.5 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (6.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ7.68-7.65 (1H, m), 7.59 (1H, d, J = 8.2 Hz), 7.52-7.49 (2H, m), 7.44 (1H, t), 7.26-7.25 (1H, m), 7.03-6.94 (4H, m), 4.97-4.94 (1H, m), 4.83-4.80 (2H, m), 4.77-4.75 (1H, m), 3.87-3.81 (1H, m), 3.60-3.03 (7H, m), 2.85-2.82 (1H, m), 2.49-2.42 (2H, m), 2.32-2.24 (8H, m), 1.75-1.62 (2H, m)

MS (ES^+) *m/z* 503.3 $(M + H)^+$.

Example 48

1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one Compound #550



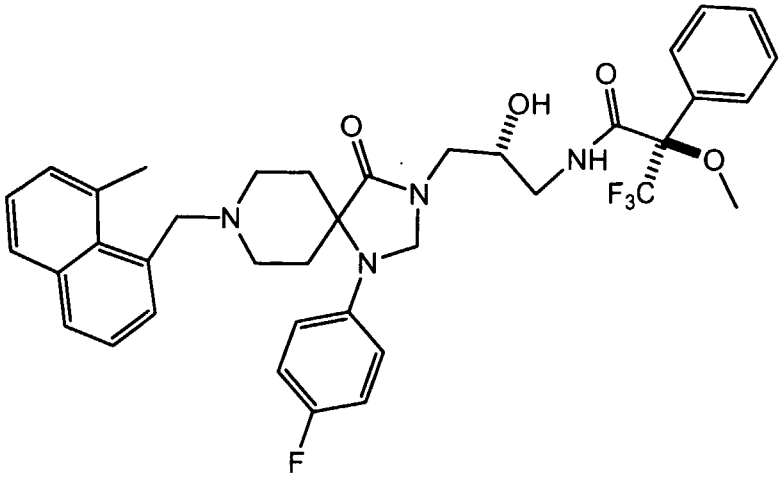
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]-decan-4-one (2.0 g, 4.95 mmol) was dissolved in N, N-dimethylformamide (25.0 mL). To the reaction mixture was then added at 0°C sodium hydride (60% in mineral oil, 238 mg, 5.94 mmol) under nitrogen atmosphere and the reaction mixture was stirred at 0°C for one hour. To the reaction mixture was then added at 0°C (2*R*)-(-)-glycidyl-3-nitrobenzenesulfonate (1.54 g, 5.94 mmol). The reaction mixture was stirred at 0°C for one hour, then at room temperature under nitrogen atmosphere for 18 hours and partitioned with water and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (2.5% methanol/dichloromethane) to yield the title compound as a foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.78-7.76 (1H, m), 7.73-7.69 (1H, m), 7.38-7.31 (4H, m), 6.99-6.91 (2H, m), 6.89-6.84 (2H, m), 4.76 (1H, d, J = 4.8 Hz), 4.65 (1H, d, J = 4.8 Hz), 4.01 (2H, s), 3.20-3.11 (6H, m), 2.86-2.77 (5H, m), 2.61-2.59 (1H, m), 2.31-2.21 (2H, m), 1.69-1.63 (2H, m)

MS (ES^+) *m/z* 460.2 $(M + H)^+$.

Example 49

3,3,3-Trifluoro-N-{3-[1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-(R)-hydroxy-propyl}-2-methoxy-2-phenyl-(R)-propionamide Compound #615



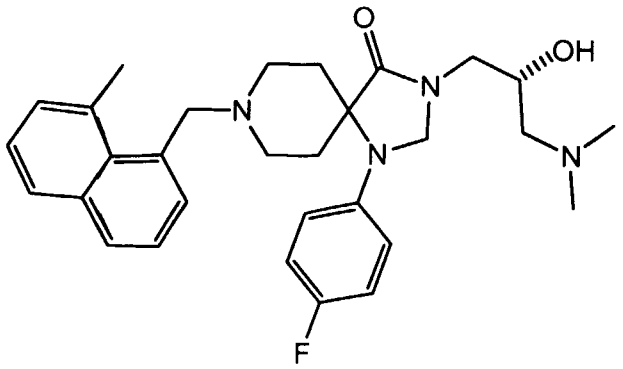
3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.0118 g, 0.024 mmol) was dissolved in dichloromethane (1.0 mL) and pyridine (0.15 mL). To the reaction mixture was then added at 0°C (S)-(+)-α-methoxy- α-(trifluoro methyl)phenyl acetyl chloride (8.7 mg, 0.034 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0°C for one hour, then the solvent was evaporated *in vacuo* to yield a crude foam. The crude foam was dissolved in ethyl acetate and successively washed twice with aqueous 0.5N HCl, twice with aqueous $NaHCO_3$, brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a white foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.64-7.61 (1H, m), 7.56-7.54 (2H, m), 7.42-7.40 (3H, m), 7.39-7.30 (3H, m), 6.97-6.93 (2H, m), 6.87-6.83 (2H, m), 4.70 (1H, d, J = 4.9 Hz), 4.64 (1H, d, J = 4.9 Hz), 3.99 (3H, s), 4.01 (1H, s), 3.60-3.54 (1H, m), 3.45-3.32 (5H, m), 3.1 (3H, s), 2.82-2.74 (4H, m), 2.24-2.20 (2H, m), 1.70-1.63 (4H, m)

MS (ES^+) *m/z* 693.0 $(M + H)^+$.

Example 50

3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #441



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.035 g, 0.07mmol) was dissolved in ethyl alcohol (2 mL). To the solution was then added a 2.0M solution of dimethylamine in methanol (1.0 mL, 2.0 mmol) and the reaction mixture was stirred at 45°C for 3 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

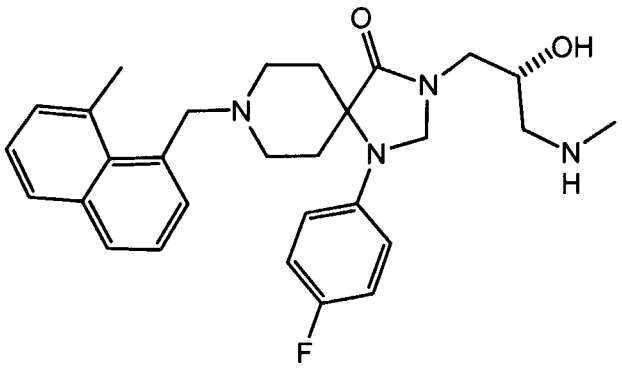
^{1}H NMR (400 MHz, $CDCl_3$) δ7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.31 (4H, m), 6.96-6.91 (2H, m), 6.88-6.84 (2H, m), 4.80 (1H, d, J = 5.1 Hz), 4.77 (1H, d, J = 5.1 Hz), 4.01 (2H, m), 3.95-3.87 (1H, m), 3.62-3.58 (1H, m), 3.31-3.26 (1H, m), 3.11 (3H, s), 2.86-2.78 (6H, m), 2.36-2.22 (9H, m), 1.68-1.63 (2H, m)

MS (ES^+) *m/z* 505.4 $(M + H)^+$.

Example 51

1-(4-Fluoro-phenyl)-3-(2-(R)-hydroxy-3-methylamino-propyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #660



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.05 g, 0.109 mmol) was dissolved in methanol (3 mL). To the solution was then added a 2.0M solution of methylamine in methanol (1.0 mL, 2.0 mmol) and the reaction mixture was stirred at 40°C for 3 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

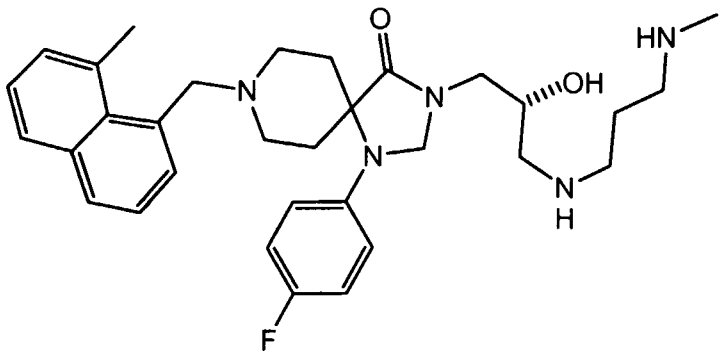
^{1}H NMR (400 MHz, $CDCl_3$) δ7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.31 (4H, m), 6.96-6.91 (2H, m), 6.88-6.84 (2H, m), 4.80 (1H, d, J = 5.1 Hz), 4.77 (1H, d, J = 5.1 Hz), 4.00 (2H, m), 3.97-3.86 (1H, m), 3.58-3.53 (1H, m), 3.43-3.35 (1H, m), 3.12 (3H, s), 2.84-2.69 (7H, m), 2.56-2.49 (1H, m), 2.44 (3H, s), 2.31-2.24 (2H, m), 1.67-1.64 (2H, m)

MS (ES^+) *m/z* 491.1 $(M + H)^+$.

Example 52

1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-methylamino-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #656



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.035 g, 0.07 mmol) was dissolved in methanol (4 mL). To the solution was then added N-methyl-1-3-propanediamine (0.027 g, 0.35 mmol) and the reaction mixture was stirred at 45°C for 12 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

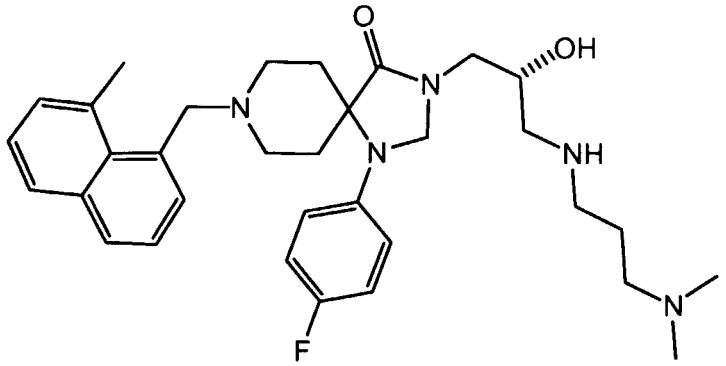
^{1}H NMR (400 MHz, $CDCl_3$) δ7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.30 (4H, m), 6.95-6.91 (2H, m), 6.87-6.84 (2H, m), 4.80 (1H, d, J = 5.05 Hz), 4.77 (1H, d, J = 5.05 Hz), 4.00 (2H, s), 3.96-3.89 (1H, m), 3.58-3.54 (1H, m), 3.32-3.30 (1H, m), 3.12 (3H, s), 2.85-2.77 (6H, m), 2.65-2.58 (1H, m), 2.49-2.12 (10H, m), 1.68-1.63 (4H, m)

MS (ES^+) *m/z* 548.3 $(M + H)^+$.

Example 53

3-[3-(3-Dimethylamino-propylamino)-2-(R)-hydroxy-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #666



1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.037 g, 0.07 mmol) was dissolved in ethanol (2 mL). To the solution was then added dimethylaminopropylamine (0.03 g, 0.3 mmol) and the reaction mixture was stirred at 45°C for 12 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

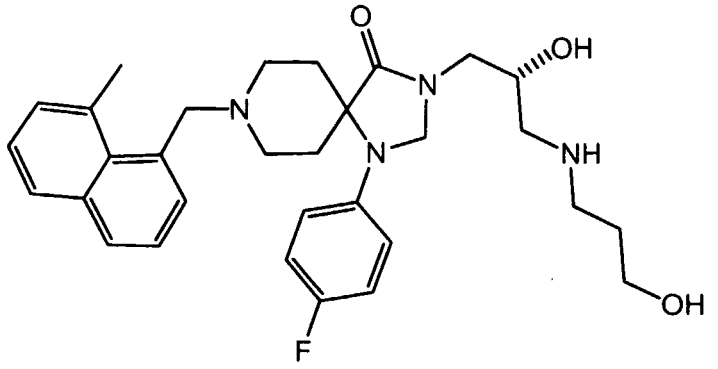
^{1}H NMR (300 MHz, $CDCl_3$) δ7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.30 (4H, m), 6.97-6.90 (2H, m), 6.87-6.82 (2H, m), 4.78-4.73 (2H, m), 4.00 (2H, s), 3.96-3.82 (1H, m), 3.59-3.53 (1H, m), 3.37-3.30 (1H, m), 3.12 (3H, s), 2.86-2.50 (9H, m), 2.35-2.11 (11H, m), 1.68-1.59 (4H, m)

MS (ES^+) *m/z* 562.2 $(M + H)^+$.

Example 54

1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxy-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #651



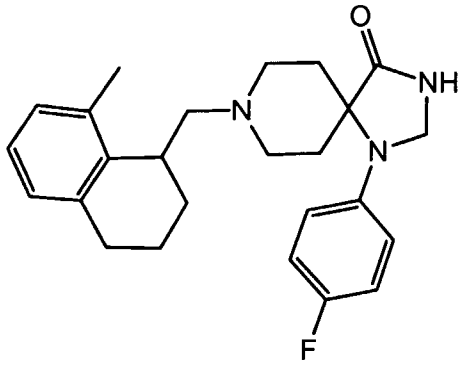
1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (1.16 g, 2.5 mmol) was dissolved in methanol (20 mL). To the solution was then added 3-amino-1-propanol (0.375 g, 5.0 mmol,) and the reaction mixture was stirred at 40°C for 12 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (5.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

^{1}H NMR (300 MHz, $CDCl_3$) δ7.78-7.75 (1H, m), 7.71-7.68 (1H, m), 7.38-7.30 (4H, m), 6.97-6.90 (2H, m), 6.87-6.82 (2H, m), 4.74-4.70 (2H, m), 3.99 (2H, s), 3.96-3.90 (1H, m), 3.81-3.77 (2H, m), 3.47-3.42 (3H, m), 3.11 (3H, s), 2.91-2.56 (10H, m), 2.30-2.20 (2H, m), 1.76-1.63 (4H, m)

MS (ES^+) *m/z* 535.2 $(M + H)^+$.

Example 55

11-(4-Fluoro-phenyl)-8-(8-methyl-1,2,3,4-tetrahydro-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #728



STEP A:

8-Methyl-1,2,3,4-tetrahydro-naphthalene-1-carboxylic acid (*J. Org. Chem.* **1982**, *47*, 2590-2593) (0.066 g, 0.34 mmol) was dissolved in tetrahydrofuran (3 mL). To the solution was then added at 0°C a 1.0M solution of borane-methyl sulfide complex in dichloromethane (0.7 mL, 0.69 mmol). The reaction mixture was stirred at room temperature for 15 minutes, refluxed for 2 hrs, then cooled down to 0°C and quenched with methanol. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was partitioned with water and diethyl ether. The organic layer was dried with

Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield crude (8-methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-methanol as an oil which was used directly to the next step.

^1H NMR (400 MHz, $CDCl_3$) δ 7.05-6.92 (3H, m), 3.70-3.59 (2H, m), 3.15-3.10 (1H, m), 2.83-2.71 (2H, m), 2.34 (3H, s), 2.21-2.16 (1H, m), 1.95-1.83 (1H, m), 1.79.1.67 (2H, m), 1.52 (1H, br s)

STEP B:

(8-Methyl-1,2,3,4-tetrahydro-naphthalen-1-yl)-methanol (0.03 g, 0.17 mmol) was dissolved in dichloromethane (0.5 mL). To the solution was then added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, also known as Dess-Martin periodinane (0.087g, 0.20 mmol). The reaction mixture was stirred for 2 hrs then partitioned with an aqueous saturated solution of thiosulfate and dichloromethane. The organic layer was washed with an aqueous saturated solution of thiosulfate, an aqueous saturated solution of sodium bicarbonate, brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield 8-methyl-1,2,3,4-tetrahydro-naphthalene-1-carbaldehyde as a solid.

^1H NMR (400 MHz, $CDCl_3$) δ 9.66 (1H, d, J=1.8 Hz), 7.13-6.99 (3H, m), 3.74-3.72 (1H, m), 2.81-2.77 (2H, m), 2.37-2.31 (1H, m), 2.2 (3H, s), 1.95-1.61 (3H, m).

STEP C:

1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.035 g, 0.14 mmol) and 8-methyl-1,2,3,4-tetrahydro-naphthalene-1-carbaldehyde (0.03g, 0.17 mmol) were dissolved in dry tetrahydrofuran (2 mL) and dry dichloromethane (0.5 mL). To the reaction mixture was then added at 0°C sodium triacetoxyborohydride (0.045g, 0.21 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via

flash chromatography (5% methanol/dichloromethane) to yield the title compound as an oil.

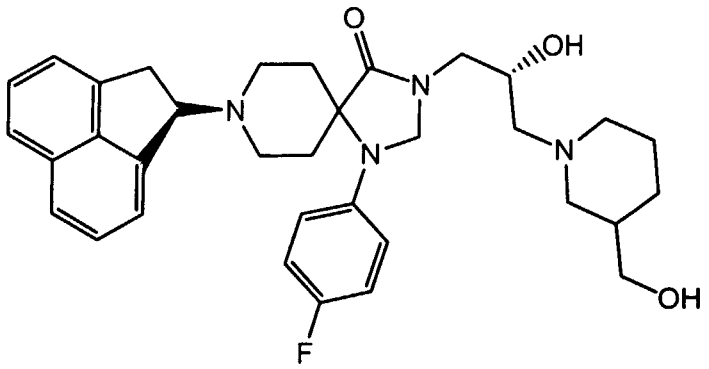
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-6.90 (7H, m), 6.56 (1H, br s), 4.68 (2H, s), 3.12-2.33 (12H, m), 1.91-1.53 (6H, m), 1.25-1.21 (2H, m)

MS (ES^+) *m/z* 408.1 $(M + H)^+$.

Example 56

(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-hydroxy-3-(3-hydroxymethyl-piperidin-1-yl)-(R)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #695



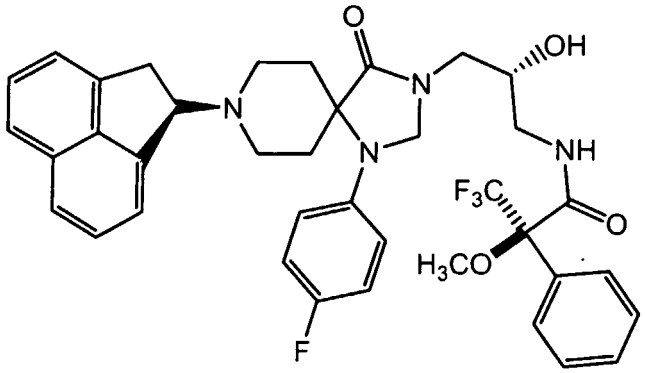
(*R*)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*S*) oxiranylmethyl-1,3,8-triaza-spiro[4.5] decan-4-one (0.02 g, 0.04 mmol) was dissolved in ethyl alcohol (1.5 mL). To the solution was then added 3-piperidinemethanol (0.01 g, 0.08 mmol) and the reaction mixture was stirred at 60°C for 12 hrs in a pressure flask. The solvent was evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (6.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ7.69-7.49 (4H, m), 7.46-7.41 (1H, m), 7.26-7.25 (1H, m), 7.04-6.95 (4H, m), 4.97-4.94 (1H, m), 4.81-4.74 (2H, m), 3.97-3.90 (1H, m), 3.58-1.6 (27H, m)

MS (ES^+) *m/z* 573.3 $(M + H)^+$.

Example 57

N-{3-[(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-4-oxo-1,3,8-triaza-spiro[4.5]dec-3-yl]-2-hydroxy-(R)-propyl}-3,3,3-trifluoro-2-methoxy-2-phenyl-(R)-propionamide Comound #645



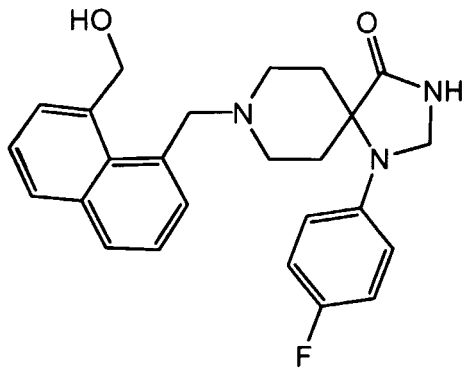
(R)-8-Acenaphthen-1-yl-3-(3-amino-2-hydroxy-(R)-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.02 g, 0.042 mmol) was dissolved in dichloromethane (3 mL) and pyridine (0.3 mL). To the reaction mixture was then added at 0°C (S)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride (13.8 mg, 0.055 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0°C for one hour, then and the solvent evaporated *in vacuo* to yield a crude foam. The crude foam was dissolved in ethyl acetate and successively washed twice with aqueous 0.5N HCl, twice with aqueous $NaHCO_3$, brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield the title compounds as a white foam.

^1H NMR (400 MHz, $CDCl_3$) δ7.68-7.59 (3H, m), 7.55-7.39 (8H, m), 7.03-6.99 (2H, m), 6.98-6.93 (2H, m), 4.95-4.92 (1H, m), 4.70 (1H, d, J = 4.8 Hz), 4.65 (1H, d, J = 4.9 Hz), 3.99-3.97 (1H, s), 3.76 (1H, s), 3.57-3.29 (5H, m), 3.08-3.00 (2H, m), 2.79-2.76 (1H, m), 2.46-2.37 (1H, m), 2.37-2.29 (1H, m), 2.24-2.16 (1H, m), 2.00 (3H, s), 1.74-1.60 (4H, m)

MS (ES^+) *m/z* 691.3 $(M + H)^+$.

Example 58

1-(4-Fluoro-phenyl)-8-(8-hydroxymethyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Comound #734



STEP A:

[8-(tert-Butyl-dimethyl-silanyloxymethyl)-naphthalen-1-yl]-methanol (*Aust. J. Chem.* **1996**, *49*, 793-800) (0.2 g, 0.66 mmol) was dissolved in dichloromethane (8 mL). To the solution was then added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, also known as Dess-Martin periodinane (0.56g, 1.32 mmol). The reaction mixture was stirred for 1 hr then partitioned with an aqueous saturated solution of thiosulfate and dichloromethane. The organic layer was washed with an aqueous saturated solution of thiosulfate, an aqueous saturated solution of sodium bicarbonate, brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (6.0% ammonia 2.0 M in methanol /dichloromethane) to yield 8-(tert-butyl-dimethyl-silanyloxymethyl)-naphthalene-1-carbaldehyde as a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.73 (1H, s), 8.05-7.98 (2H, m), 7.86-7.84 (1H, m), 7.65-7.63 (1H, m), 7.55-7.48 (2H, m), 5.07 (2H, s), 0.83 (9H, s), 0.01 (6H, s)

STEP B:

1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.056 g, 0.22 mmol) and 8-(tert-butyl-dimethyl-silanyloxymethyl)-naphthalene-1-carbaldehyde (0.067 g, 0.22 mmol) were dissolved in dry 1,2-dichloroethane (5 mL). To the reaction mixture was added crashed 4A Molecular Sieve (0.028 g), a catalytic amount of glacial acetic acid. The reaction mixture was stirred at room temperature for I hr and it was then added at room temperature sodium triacetoxyborohydride (0.071 g, 0.33 mmol) under nitrogen atmosphere and the

reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was then partitioned with water and dichloromethane. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via semi-preparative HPLC (aqueous 0.5% TFA/acetonitrile) to yield crude 8-[8-(tert-butyl-dimethyl-silanyloxymethyl)-naphthalen-1-ylmethyl]-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one which was directly used to the next step.

STEP C:

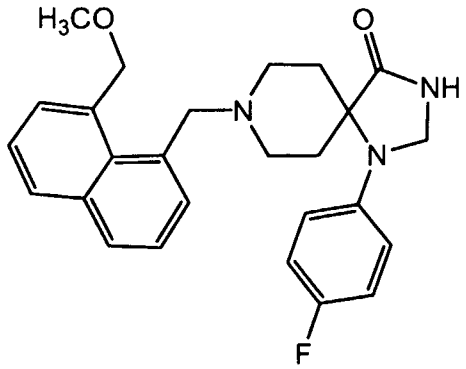
To the crude intermediate prepared as in STEP B was added acetonitrile (5 mL) and aqueous 5% TFA (5 mL). The reaction mixture was stirred at room temperature for 6 hrs. The solvent was then evaporated *in vacuo* to yield the title compound as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (1H, br s), 7.86-7.81 (2H, m), 7.53-7.51 (1H, m), 7.43-7.33 (3H, m), 6.98-6.92 (2H, m), 6.84-6.79 (2H, m), 6.55 (1H, s), 5.12 (2H, br s), 4.66 (2H, s), 4.33 (1H, br s), 3.03-2.93 (4H, m), 2.38-2.31 (2H, m), 1.79-1.75 (2H, m)

MS (ES^+) *m/z* 420.1 $(M + H)^+$.

Example 59

1-(4-Fluoro-phenyl)-8-(8-methoxymethyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #733



STEP A:

(8-Methoxymethyl-naphthalen-1-yl)-methanol (*Tetrahedron Lett.* **1997**; *38*, 8161-8164) (0.36 g, 1.8 mmol) was dissolved in dichloromethane (10 mL).

To the solution was then added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, also known as Dess-Martin periodinane (1.5 g, 3.6 mmol). The reaction mixture was stirred for 1 hr, then partitioned with an aqueous saturated solution of thiosulfate and dichloromethane. The organic layer was washed with an aqueous saturated solution of thiosulfate, an aqueous saturated solution of sodium bicarbonate, brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield crude 8-methoxymethyl-naphthalene-1-carbaldehyde which was used directly into the next step.

STEP B:

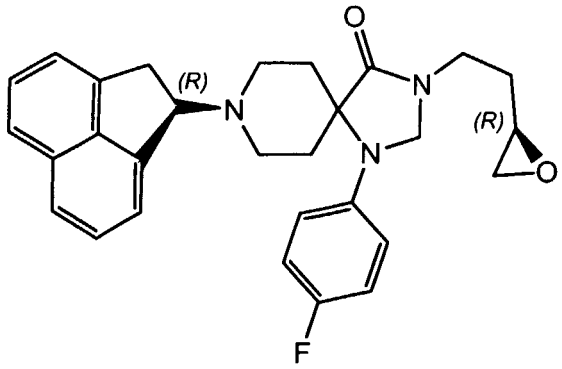
1-(4-Fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.45 g, 1.8 mmol) and crude 8-methoxymethyl-naphthalene-1-carbaldehyde (0.35 g, 1.8 mmol) were dissolved in dry dichloromethane (25 mL), dry 1,2-dichloroethane (5 mL) and glacial acetic acid (0.5 mL). The reaction mixture was stirred at room temperature for 1 hr. To the reaction mixture was then added, at room temperature, sodium triacetoxyborohydride (0.57 g, 2.7 mmol) under nitrogen atmosphere and the reaction mixture was stirred at room temperature for 4 days. The reaction mixture was partitioned with water and dichloromethane. The organic layer was washed with brine, dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (40% ethyl acetate in hexanes) to yield the title compound as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.80 (2H, m), 7.60-7.58 (1H, m), 7.49-7.37 (3H, m), 6.94-6.83 (4H, m), 6.12 (1H, s), 5.23 (2H, s), 4.64 (2H, s), 4.10 (2H, s), 3.38 (3H, s), 2.91-2.81 (4H, m), 2.30-2.23 (2H, m), 1.73-1.70 (2H, m)

MS (ES^+) *m/z* 434.2 $(M + H)^+$.

Example 60

(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(2-(R)--oxiranyl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #723



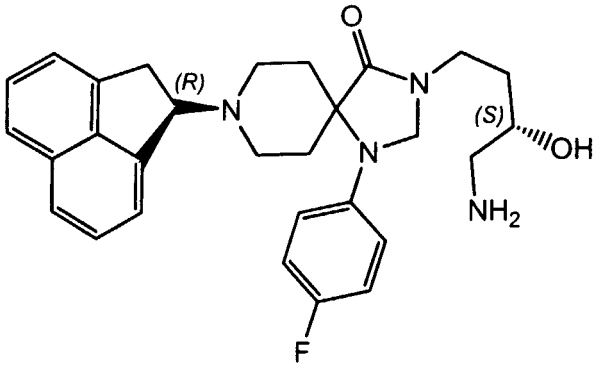
(*R*)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.25 g, 0.62 mmol) was dissolved in N, N-dimethylformamide (2.0 mL). To the reaction mixture was then added at 0°C sodium hydride (60% in mineral oil, 0.03 g, 0.80 mmol) under nitrogen atmosphere. The reaction mixture was stirred at 0°C for 30 minutes. To the reaction mixture was then added, at 0°C, 2-(R)-(2-bromo-ethyl)-oxirane (0.14 g, 0.93 mmol). The reaction mixture was stirred at 0°C under nitrogen atmosphere for 1 hr, then room temperature for 18 hours and then partitioned with water and ethyl acetate. The organic layer was dried with Na_2SO_4, filtered and the solvent evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (6% methanol / dichloromethane) to yield the title compound as a foam.

^{1}H NMR (400 MHz, $CDCl_3$) δ7.70-7.65 (1H, m), 7.59 (1H, d, J = 8.2 Hz), 7.54-7.50 (2H, m), 7.43 (1H, t), 7.26 (1H, d), 7.04-6.93 (4H, m), 4.95 (1H, dd, J = 3.4 and 7.8 Hz), 4.64 (2H, dd, J = 4.3 and 10.7 Hz), 3.64-3.50 (3H, m), 3.38-3.31 (1H, m), 3.19-3.03 (2H, m), 2.97-2.92 (1H, m), 2.83-2.80 (1H, m), 2.75-2.73 (1H, m), 2.48-2.39 (3H, m), 2.29-2.21 (1H, m), 2.03-1.95 (1H, m), 1.75-1.62 (3H, m)

MS (ES^+) *m/z* 472.2 $(M + H)^+$.

Example 61

(R)-8-Acenaphthen-1-yl-3-(4-amino-3-(S)-hydroxy-butyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #722



(R)-8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(2-(R)-(oxiranyl-ethyl)-1,3,8-triaza-spiro[4.5]decan-4-one (0.03 g, 0.06 mmol) was dissolved in ethyl alcohol (1.0 mL). To the solution was then added concentrated ammonium hydroxide (1.0 mL) and the reaction mixture was stirred at 40°C for 7 hrs in a pressure flask. The solvent was then evaporated *in vacuo* to yield a crude oil. The crude oil was purified via flash chromatography (6.0% ammonia 2.0 M in methanol /dichloromethane) to yield the title compound as a foam.

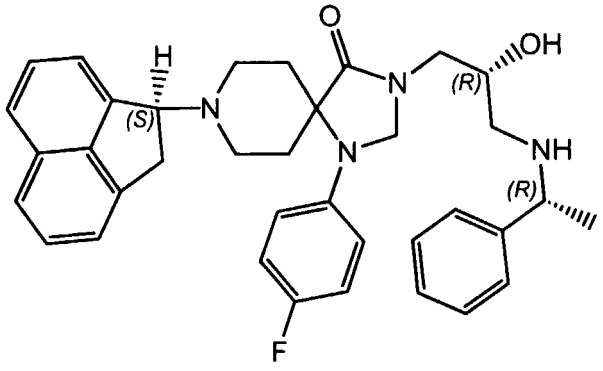
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.65 (1H, m), 7.59 (1H, d, J = 8.2 Hz), 7.54-7.50 (2H, m), 7.43 (1H, t), 7.26 (1H, d), 7.04-6.93 (4H, m), 4.96-4.94 (1H, m), 4.64 (2H, dd, J = 4.3 and 10.7 Hz), 3.86-3.76 (1H, m), 3.57-3.45 (2H, m), 3.39-2.98 (4H, m), 2.85-2.76 (2H, m), 2.65-2.58 (1H, m), 2.52-2.40 (2H, m), 2.32-2.24 (1H, m), 2.10-1.90 (3H, m), 1.76-1.51 (4H, m)

MS (ES^+) m/z 489.1 $(M + H)^+$.

Example 62

8-(S)-Acetonaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-(R)-hydroxy-3-(1-phenyl-ethylamino)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one

Compound #663



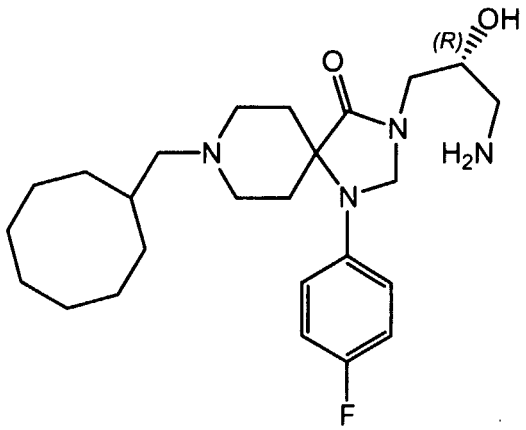
8-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-(*S*)-oxiranylmethyl-1,3,8-triaza-spiro[4.5] decan-4-one (0.45 g, 0.98 mmol) and R-(+)-α-methylbenzyl amine (0.178 g, 1.47 mmol) were dissolved in ethanol (3 mL). The reaction mixture was heated at 120°C and microwaved for 600 sec. The solvent was evaporated *in vacuo* to yield an oil. The crude oil was purified via flash chromatography (80% ethyl acetate/heptane) to yield the title compound as a solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, t), 7.60 (1H, d, *J* = 8.2 Hz), 7.50-7.54 (2H, d, *J* = 5.1 Hz), 7.44 (1H, t), 7.07-7.28 (6H, m), 6.8-7.0 (4H, m), 4.9 (1H, m), 4.6 (2H, s), 3.8 (2H, m), 3.25-3.55 (5H, m), 2.95-3.1 (2H, m), 2.78-2.82 (1H, m), 2.6 (1H, m), 2.1-2.4 (5H, m), 1.5 (2H, m), 1.3 (3H, d)

MS (ES^+) *m/z* 579.2 (MH+), 427.2

Example 63

3-(3-Amino-2-(R)-hydroxy-propyl)-8-cyclooctylmethyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one Compound #620



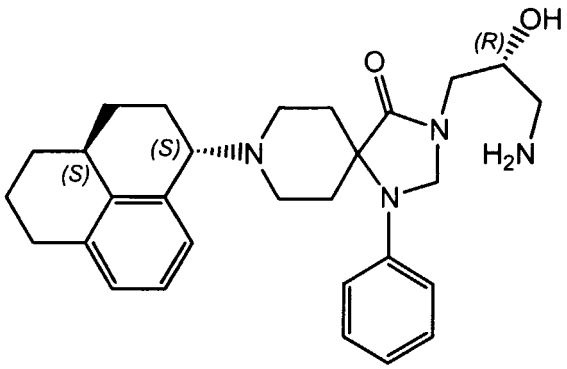
Cyclooctylmethyl-1-(4-fluoro-phenyl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (0.71 g, 1.65 mmol) was dissolved in absolute ethanol (5 mL), then mixed with ammonium hydroxide (2 mL, 14.4 mmol) and heated to 120°C and microwaved for 600 sec. The solvent was evaporated and the resulting residue was purified by column chromatography (80% ethyl acetate/heptane) to yield the title compound as an oil.

MS (electrospray) = 447.4 (MH+)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.1-1.3 (m, 2H), 1.4-1.8 (m, 16 H), 2.1 (d, 2H), 2.2-2.38 (m, 2H), 2.6-2.8 (m, 5H), 2.8-3.0 (m, 2H), 3.3-3.6 (m, 2H), 3.7-3.8 (m, 2H), 4.7 (s, 2H), 6.8-7.0 (m, 4H).

Example 64

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-1,3,8-triaza-spiro[4.5]decan-4-one dihydrochloride Compound #640



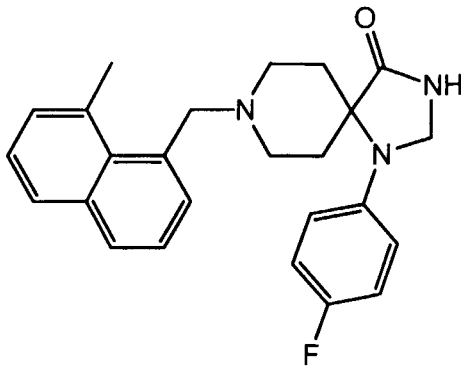
1-(4-Fluoro-phenyl)-8-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-3-(S)-oxiranylmethyl-1,3,8-triaza-spiro[4.5]decan-4-one (60 mg, 0.131mmol) was dissolved in absolute ethanol (1 mL), then mixed with ammonium hydroxide (0.3 mL) and heated to 120°C and microwaved for 480 sec. The solvent was evaporated. The resulting residue was dissolved in ethyl acetate and then treated with HCl in diethyl ether (1M, 1 mL) to yield the title compound as a solid.

MS (electrospray) = 475.2 (MH+), 305.1

1H NMR (300 MHz, CD_3OD) δ 0.9-1.0 (m, 1H), 1.1-1.5 (m, 5H) 1.7-1.8 (m, 1H), 2.0-2.25 (m, 6H), 2.3-2.7 (m, 4H), 2.7-3.2 (m, 7H), 3.32-3.7 (m, 2H), 3.85-4.2 (m, 2H), 4.9 (m, 2H), 6.9-7.4 (m, 8H)

Example 65

1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]-decan-4-one Compound #547



STEP A: (8-Hydroxymethyl-naphthalen-1-yl)-methanol

A 12-L 4-neck flask equipped with a thermocouple, an overhead stirrer, a 2-L addition funnel, and a condenser under N_2 was charged with 1,8-naphthalic anhydride (200 g, 1.0 mol) in toluene (2.5 L) at room temperature. The reaction mixture was agitated while adding DIBAL-H (1.5 M in toluene, 2.664 L, 4 mol) via the addition funnel over 1.5 h. The solution was then heated to 95°C overnight, cooled to 15°C and then slowly diluted with ethyl acetate (2.2 L) and H_2O (2 L) followed by addition of concentrated HCl (320 mL). The resulting suspension was stirred for 30 min at room temperature, filtered, and air dried on the filter for 2 h. The resultant material was in 95% ethanol (1.2 L), stirred at 70°C for 2 h, and filtered to yield a wet solid which was air dried overnight on the filter and then dried at 70°C in a vacuum oven to yield (8-hydroxymethyl-naphthalen-1-yl)-methanol as a solid;

^{1}H NMR (400 MHz, CD_3OD) δ7.85 (2H, dd, J = 1.3 and 8.2 Hz), 7.61 (2H, dd, J = 1.0 and 7.0 Hz), 7.46-7.42 (2H, m), 5.22 (2H, s), 4.82 (4H, s).

STEP B: 1*H*,3*H*-Benzo[*de*]isochromene

A 1-L 3-neck flask equipped with an overhead stirrer, a condenser, and a thermocouple was charged with (8-hydroxymethyl-naphthalen-1-yl)-methanol (33.0 g, 0.175 mol), concentrated phosphoric acid (225 mL), and water (5 mL). The reaction mixture was stirred at 140°C for 3 h, cooled to room temperature, diluted with CH_2Cl_2 (800 mL) and transferred to a 2-L separatory funnel. After washing the organic layer with water and saturated $NaHCO_3$ it was dried over $MgSO_4$ and evaporated to yield 1*H*,3*H*-Benzo[*de*]isochromene as a solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.96-6.92 (2H, m), 6.62-6.58 (2H, m), 6.39-6.37 (2H, m), 4.17 (3H, s).

STEP C: (8-Methyl-naphthalen-1-yl)-methanol (See *Tetrahedron*, 2000, 56, 8375-8382)

A 3-L 4-neck flask equipped with an overhead stirrer, a thermocouple, a condenser, a nitrogen inlet, and a 1-L addition funnel was charged with potassium (30 g, 0.764 mol) and THF (1 L). The metal suspension was heated to 60°C for 30 min and then stirred to room temperature. To the reaction mixture was then added naphthalene (2 g, 0.015 mol), the suspension was stirred at room temperature for 10 min and then cooled to -20°C to afford a blue suspension. A solution of 1*H*,3*H*-Benzo[*de*]isochromene (26 g, 0.153 mol) in THF (500 ml) was slowly added via the addition funnel, with addition controlled so that the reaction temperature did not exceed –15°C. After stirring for 5 h at –20°C, the suspension was removed from the cooling bath, warmed with stirring to 0°C, and then allowed to stand without stirring (potassium metal settling). The solution was decanted and the residual potassium was cooled and carefully decomposed with isopropyl alcohol (IPA) under N_2. The decanted solution was carefully treated with water (20 mL) under nitrogen and stirring was continued for 20 min. Additional water and ether were added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried over $MgSO_4$ and condensed *in vacuo* to yield a crude material. The crude material was purified by flash chromatography (7.5/2.5 hexane/EtOAc) to yield 8-methyl-1-napthalenemethanol as a solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.82-7.80 (1H, m), 7.73-7.69 (1H, m), 7.52-7.50 (1H, m), 7.41-7.32 (3H, m), 5.17 (2H, bs), 3.01 (3H, s).

STEP D: 8-Methyl-naphthalene-1-carbaldehyde

A 1-L 4-neck equipped with an overhead stirrer, a condenser and a thermocouple was charged with 8-methyl-1-napthalenemethanol (18.5 g, 0.107 mol) in CH_2Cl_2 (500 mL) and stirred at room temperature under N_2. Solid

$Mn_{(IV)}O_2$ (61 g, 0.7 mol) was carefully added and the reaction was stirred at room temperature for 3 h, then at 40°C for 6 h and then at room temperature overnight. The reaction mixture was diluted with CH_2Cl_2 (500 mL), filtered and the filtrate was washed with 1N HCl and then dried over $MgSO_4$. The resulting crude material was purifed using silica gel chromatography (8/2 hexane/ethyl acetate) to yield 8-methyl-naphthalene-1-carbaldehyde as a solid.

^1H NMR (400 MHz, $CDCl_3$) δ 10.92 (1H, s), 8.04 (1H, dd, J = 1.3 and 8.1 Hz), 7.96 (1H, dd, J = 1.4 and 7.1 Hz), 7.82-7.73 (1H, m), 7.55-7.51 (1H, m), 7.49-7.44 (2H, m), 2.82 (3H, s)

STEP E: 1-(4-Fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]-decan-4-one.

A 1-L 3-neck flask equipped with an overhead stirrer and a thermocouple was charged with 8-methyl-naphthalene-1-carbaldehyde (13.75 g, 0.08 mol) and 1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one (21.5 g, 0.085 mol) under N_2 in CH_2Cl_2 (500 mL). After stirring for 20 min, HOAc (1 mL) was added followed by careful addition of solid $NaBH(OAc)_3$ (33.4 g, 0.157 mol). The mixture was stirred for 16 h at room temperature (suspension becomes a solution). The reaction was then warmed at 50°C for 2 h, cooled down to room temperature and then treated with 0.5 N NaOH (50 mL), stirred for 10 min and then diluted with CH_2Cl_2 (100 mL). The organic layer was isolated and dried over $MgSO_4$. The solvent was evaporated to yield a residue, which was suspended in diethyl ether, stirred for 20 min, filtered and dried in a 60°C vacuum oven to yield 1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]-decan-4-one as a white solid;

^1H NMR (400 MHz, $CDCl_3$) δ 7.79-7.76 (1H, m), 7.72-7.69 (1H, m), 7.39-7.30 (4H, m), 6.98-6.92 (2H, m), 6.87-6.82 (2H, m), 6.24 (1H, br s), 4.66 (2H, s), 4.01 (2H, s), 3.12 (3H, s), 2.86-2.78 (4H, m), 2.33-2.23 (2H, m), 1.72 (2H, d, J = 14.1 Hz);

MS (ES^+) m/z 404.2 $(M + H)^+$.

Elemental Analysis

Calculated: C: 69.26%, H: 7.06%, N: 11.34%, F: 3.91%, H_2O: 1.85%

Measured: C: 68.96%, H: 6.83%, N: 11.38%, F: 4.00%, H_2O: 0.58%

Example 66

Production of Cells Expressing the ORL-1, Delta, Kappa or Mu Receptor

HEK293 cells were transfected with nociceptin receptor (ORL-1, human mRNA GenBank #AF348323) or any of the opioid receptor subtype delta (δ, human mRNA Genbank #U07882) kappa (κ, human mRNA Genbank #U17298) and mu (μ, human mRNA Genbank #L29301). The vector used was pCi-neo (G418 selection). The transfections were performed with LipofectAMINE 2000 (Life Technologies Cat. # 11668-019) using the following procedure.

The day before transfection, a 24 well plate was inoculated with $2X10^5$ cells per well in 0.5 ml of normal growth medium (MEM + EBSS + NEAA + 10% BCS). Two wells were prepared for each specialty along with a no DNA control. For each well transfected, 0.8μg of DNA was diluted into 50μl (total volume) of OPTI-MEM I Reduced Serum Medium (Life Technologies Cat. # 51985-034). For each well transfected, 2 μl of LipofectAMINE 2000 (LF2000) was diluted into 50μl (total volume) of OPTI-MEM I medium and incubated for 5 minutes at room temperature. The diluted DNA and LF2000 were combined and incubated at room temperature for 20 minutes. The growth medium was aspirated from each well and replaced with 1ml of OPTI-MEM I. A total of 100 μl of the DNA-LF2000 complexes were added to each well and mixed with gentle swirling. The plate was incubated at 37°C, 5% CO_2 for 5 hours. The OPTI-MEM I medium was aspirated from each transfected well and replaced with 1 ml growth medium. The plate was returned to the incubator for 24 hours. The wells were trypsinized and cells added to 100 mm tissue culture dishes (2 dishes per well). The dishes were incubated for 24 hours. The medium was aspirated from each dish and replaced with growth medium containing 400μg/ml Geneticin (G418) selective antibiotic. The plates were refer every 3-4 days.

Distinct colonies appeared in approximately 3 weeks. One week later, 48 out of approximately 100 colonies per dish were subcultures to 1 well each of two 24 well plates containing 1 ml of selective medium per well.

Confluent wells were expanded to 6 well plates, then T25 flasks and T75 flasks. Cell lines showing poor growth patterns were eliminated. Membranes were prepared from each cell line and receptor activity determined by a receptor binding assay.

EXAMPLE 67

Method for measuring affinity for the ORL-1 receptor

The nociceptin receptor binding assay measures the binding of ^{125}I-Tyr^{14}-nociceptin (2200 Ci/mmol, New England Nuclear) to human nociceptin receptor (ORL-1) on HEK293 cell membranes.

HEK293 cell membrane (prepared as described in Pulito, V.L. *et al.*, 2000, *J. Pharmacol. Exp. Ther.* **294**, 224-229), with the exception that the buffer used was a mixture of 50 mM Tris-HCl pH7.8, 5 mM $MgCl_2$ and 1 mM EGTA), was added to PEI treated WGA FlashPlates (New England Nuclear) at 1 µg/well in binding buffer of 50 mM Tris-HCl pH 7.8, 5 mM $MgCl_2$ and 1 mM EGTA. ^{125}I-Tyr^{14}-nociceptin was added at a final concentration of 0.5 nM and the volume adjusted to 50 µl with binding buffer. The plate was incubated for two hours at room temperature, the reactions were aspirated and the wells washed two times with 200 µl binding buffer and then filled with 200 µl binding buffer. The plates were then sealed and counted on a Packard Top Count to determine radioactivity bound to the membranes.

For each test compound, the total binding (%Inh) was measured at several concentrations and the IC_{50} (the concentration at which 50% of the binding is inhibited) was determined from the graphical display of X = logarithm of concentration versus Y = response, using the following calculation:

$$Y = (\text{Minimum}) + \frac{(\text{Maximum-Minimum})}{(1+10^{\log(EC_{50}-X)})}$$

For some of the test compound, Ki was determined, using the following calculation:

Ki values were calculated using Graphpad Prizm software, where

$$Ki = (IC_{50}) / (+[radioligand]/Kd)$$

For the ORL-1 binding, the Kd was 0.5nM. The [radioligand] used was the same as the Kd.

The ability of representative compounds of the present invention to bind to the ORL-1 receptor in a HEK cell line using a radio-labelled nociceptin as the displaceable ligand was determine according to the procedure described above with results as listed in Table 12. (Note that for the compounds which were tested more than once, the value listed in Table 12 is the calculated mean.)

TABLE 12

ID#	ORL-1 IC_{50} (nM)	ORL-1 Ki (nM)
1	8.10	
2	8.49	
3	173.0	
4	3.63	
5	20.1	
6	4.66	
7	13.4	
8	4.86	
9	233.0	
10	10.5	
11	22.3	
12	21.0	
13	10.6	
14	25.2	
15	31.8	
16	122.0	
17	10.8	
18	10.3	
19	15.0	
20	15.8	
21	9.22	
22	20.7	
23	80.5	
24	34.8	
25	33.0	

26	20.3	
27	11.0	
28	7.74	
29	121.0	
30	23.2	
31	44.5	
32	13.7	
33	95.3	
34	26.9	
35	30.3	
36	8.73	
38	8.88	
39	149.0	
40	9.40	
41	8.32	
42	19.2	
43	19.9	
44	43.1	
45	6.45	
46	16.2	
47	0.86	
48	1.28	
49	14.8	
50	298.0	
51	259.0	
52	0.48	
53	0.47	
54	3.03	
55	2.75	
56	4.70	
57	20.0	
58	476.0	
59	94.5	
60	396.0	
61	1.09	
62	0.78	
63	19.2	
64	33.9	
65	88.5	
66	39.2	
67	12.2	
68	10.4	
69	20.5	
70	72.9	
71	59.3	
72	82.6	
73	14.0	
74	8.08	

75	21.1	
76	16.1	
78	18.0	
79	18.2	
100	4.10	
101	1.79	
102	199.0	
103	18.5	
104	0.72	
105	81.6	
106	55.4	
107	57.7	
108	36.9	
110	45.0	
111	25.2	
112	18.0	
113	27.4	
114	15.1	
115	14.0	
116	17.0	
117	99.7	
119	2.8	
121	39.9	
122	32.4	
123	61.2	
124	41.6	
125	44.1	
126	38.6	
127	61.0	
128	38.6	
129	160.0	
130	48.8	
131	17.0	
132	33.9	
133	108.0	
134	329.0	
135	17.3	
136	1330.0	
137	101.0	
138	31.9	
139	139.0	
140	108.0	
141	26.0	
142	49.9	
143	39.7	
144	40.0	
145	12.8	
146	85.6	

147	34.3	
148	81.1	
149	40.9	
150	28.5	
151	10.9	
152	37.6	
153	60.4	
154	6.96	
155	98.9	
156	21.8	
157	43.5	
158	41.9	
159	298.0	
160	53.5	
161	90.7	
162	46.0	
163	539.0	
164	252.0	
165	54.5	
166	52.2	
167	45.5	
168	151.0	
169	219.0	
170	>10,000	
171	19.9	
173	31.8	
174	68.7	
175	86.3	
176	51.3	
177	166.0	
178	62.2	
179	33.0	
180	116.0	
181	67.3	
182	7.7	
183	40.0	
187	17.1	
188	7.1	
189	7.6	
190	41.0	
191	10.7	
192	4.2	
193	14.0	
194	7.00	
197	2.00	
198	46.0	
203	1.3	
204	30.9	

205	17.5	
206	8.0	
208	10.7	
209	33.00	
210	3.10	
211	2.90	
215	9.35	
217	12.7	
218	6.6	
219	6.6	
220	100.0	
224	9.00	
225	7.3	
227	25.0	
228	3.3	
229	7.6	
230	105.0	
250	59.7	
251	10.5	
252	35.2	
253	20.4	
254	16.3	
255	66.5	
256	23.5	
257	14.9	
258	343.0	
259	199.0	
260	560.0	
261	54.1	
262	182.0	
263	86.7	
264	283.0	
265	366.0	
266	471.0	
267	178.0	
268	147.0	
269	157.0	
270	148.0	
271	0.70	
275	1.19	
276	7.97	
280	118.0	
281	8.90	
282	6.35	
283	13.9	
284	7.86	
285	78.3	
289	7.05	

290	14.2	
291	17.5	
292	462.5	
293	279.0	
294	1360.0	
295	0.52	
296	1.78	
298	0.87	
299	3.06	
300	0.89	
305	0.996	
307	2.22	
308	1.99	
309	0.36	
310	10.7	
311	0.83	
312	1.16	
313	6.03	
314	1.37	
315	0.78	
316	1.01	
317	1.06	
318	0.87	
319	3.44	
320	1.70	
321	0.65	
322	0.51	
323	0.82	
324	2.51	
325	1.64	
326	0.74	
327	0.23	
328	4.55	
329	2.02	
330	0.91	
331	0.90	
332	0.41	
333	1.68	
334	0.53	
335	0.40	
336	0.50	
337	1.40	
338	0.82	
339	0.75	
340	0.12	
341	0.30	
342	135.0	
343	1.05	

344	1.92	
345	0.24	
346	0.72	
347	2.72	
348	0.66	
349	0.90	
350	0.58	
351	0.81	
352	1.55	
353	0.42	
354	0.92	
355	2.13	
356	0.57	
358	0.10	
360	0.25	
362	2.37	
364	1.67	
365	1.30	
366	1.59	
367	4.05	
368	5.54	
370	2.10	
371	2.96	
372	1.13	
373	3.48	
374	20.9	
375	3.93	
376	0.85	
377	0.82	
378	0.56	
379	0.17	
380	1.03	
381	0.28	
382	0.80	
383	0.32	
385	135.0	
386	111.0	
387	37.8	
388	30.5	
389	106.0	
390	69.7	
391	51.5	
392	121.0	
393	6.68	
394	198.0	
395	130.0	
396	23.1	
398	77.5	

399	65.8	
418	79.5	
419	1.17	
420	0.33	
421	0.26	
422	13.6	
423	0.34	
424	0.23	
425	1.01	
426	2.19	
427	3.23	
428	2.48	
429	2.53	
430	2.64	
431	2.07	
432	3.41	
433	1.95	
434	1.02	
435	0.78	
436	0.99	
437	1.24	
438	49.6	
439	34.2	
440	22.7	
441	70.5	
442	27.4	
443	1.19	
444	1.18	
445	1.78	
446	1.98	
447	17.9	
448	2.02	
451	6.35	
452	29.0	
453	39.4	
454	4.71	
455	183.0	
456	462.0	
457	377.0	
458	35.9	
459	128.0	
460	42.7	
461	1.32	
462	1.54	
463	1.44	
464	0.81	
465	0.16	
500	0.74	

501	567.0	
502	3920.0	
503	563.0	
504	39.3	
505	9770	
506	493.6	
507	23.9	
508	383.0	
509	0.36	
510	165.0	
511	35.7	
512	1.02	
513	254.0	
514	20.8	
516	>10,000	
517	>10,000	
518	19.0	
519	24.4	
520	84.0	
521	>10,000	
522	213.4	
523	>10,000	
524	>10,000	
525	>10,000	
526	>10,000	
527	>10,000	
528	>10,000	
529	>10,000	
530	>10,000	
531	>10,000	
532	>10,000	
533	>10,000	
534	>10,000	
535	5720	
536	4300	
537	569.	
538	>10,000	
539	>10,000	
541	897	
542	283	
543	2640	
544	204.0	
546	3530	
547	42.6	
548	132.0	
549	1220	
550	13.5	
551	37.4	

552	92.0	
553	11.0	
554	80.4	
555	0.25	
556	1.27	
564	0.22	
565	0.38	
566	0.77	
567	1.41	
568	1.36	
569	0.83	
570	0.24	
571	0.23	
572	5600	
573	896	
576	0.46	
578	164.0	
579	0.83	
581	9.00	
582	40.00	
600	1.11	
601	7.59	
602	1.11	
603	1.98	
604	2.06	
605	0.81	
606	1.03	
607	3.05	
608	10.00	
609	10.00	
610	10.00	
611	0.37	
612	1.85	
613	0.83	
614	1.69	
616		17.95
617		5.83
618		6.23
619		30.21
620		6.16
621		5.05
623		19.77
624		5.83
625		5.50
626		158.30
627		4.66
628		20.21
629		19.58

633		18.87
634		6.49
635		4.80
636		6.08
637		2.26
638		4.30
639		0.11
640		0.61
641		0.28
642		0.43
643		0.47
644		0.42
647		0.44
648		320.4
649		35.44
650		21.43
651		5.87
652		17.34
653		177.1
654		1.10
655		26.55
656		8.17
657		2.18
658		0.32
659		0.75
660		19.2
661		25.74
662		29.86
663		1.60
664		117.90
665		44.36
666		8.02
667		0.04
668	3.25	
669	1.40	
670	10.00	
671	10.00	
672	10.00	
673	10.00	
674	10.00	
675		25.49
677		56.99
678		6.73
679		0.53
680		115.7
681		7.54
682	10.00	
683	10.00	

684	10.00	
685	10.00	
686	10.00	
687		18.68
688		76.33
689		25.05
690		23.51
691	0.35	
692		0.48
693	0.37	
694	0.46	
695	0.19	
696	0.29	
697	0.34	
698	0.26	
699	0.55	
700	0.94	
701	0.52	
702	0.84	
703	0.72	
704		20.11
705		11.78
706		15.04
707		13.72
708		9.42
709		17.45
710		23.32
711		17.87
712		27.59
713		4.87
714		27.61
715		5.16
716		5.76
717		5.25
718		4.41
719		4.34
720		5.21
721		17.62
722	0.57	
723	0.88	
726		10.58
727		75.12
728		104.9
729		476.6
733		3.77
734		72.8

EXAMPLE 68

Filtration Binding Assay: ORL-1, Mu, Kappa and Delta opioid receptors.

The assay used to measure the binding of representative test compounds to the ORL-1, delta, kappa and mu opioid receptors was run similarly, with appropriate selection and substitution of cell membrane and radiolabeled ligand. The following cell membranes and ligands were used for the determination of binding to the respective opioid receptors.

ORL-1 (Nociceptin)	1 ug/well of 3C4 cell line membrane and 0.5nM final concentration of ^{125}I nociceptin
Delta (δ) opioid:	1 μg/well of 2D4 cell line membrane and a final concentration of 2.44 nM DPDPE-^{3}H ligand.
Mu (μ) opioid:	5 μg/well of 1D4 cell line membrane and a final concentration 0.8993 nM DAMGO-^{3}H ligand.
Kappa (κ) opioid:	7 μg/well of 2C2 cell line membrane and a final concentration of 2.76 nM U-69,593-^{3}H ligand.

Both membrane and ligand were diluted such that a 25 μl addition delivered the necessary amount per well, as noted above. Both membrane and ligand were diluted in 1X ORL-1 buffer. The ORL-1 buffer was composed of 50 mM Tris-HCl, pH = 7.4, 5 mM $MgCl_2$ and 1 mM EGTA. Each test compound was diluted to a concentration in the range of from 100 μM to 10 pM (half-log curve) with 100% DMSO. To each well of a 96 well plate was added 25μL cell membrane (as listed above), 1μL of the diluted test compound, and 25μL labeled ligand (as listed above) for the mu, delta, kappa or ORL-1 opioid receptor, as desired.

The plate was incubated on a rotating shaker for 2 hours at room temperature. The plate was filtered over GF/C Filterplates, prewetted in 0.03%

polyethleneimine, in Filtermate 196 apparatus (Packard). The plate was then washed 6 times with ORL-1 buffer in the filtration apparatus and dried in vacuum oven for 1 hour at a temperature of 50°C.

To each well was then added 25µL Microscint 20 (Packard) (to solubilize bound radioactivity) and each well counted in a Packard TopCount for 1 minute/well using counting parameters optimized for the particular radioligand / opioid receptor being tested. Percent radioactive ligand bound in each reaction was calculated relative to a control using DMSO for maximum binding (no inhibition). Curves were fitted and K_i's determined using Graphpad Prizm software (v3.0). The K_is were calculated using the following formula by Graphpad Prizm software, where

$$Ki = (IC_{50}) / (1+[radioligand]/K_d)$$

For the ORL-1, the K_d is 0.5nM, for Mu it is 0.8993 nM, for kappa it is 2.76 nM and for delta it is 2.44 nM. Note that the [radioligand] (concentration of radioligand) was equivalent to the K_d.

Representative compounds of the present invention were tested for binding to the mu, kappa and delta opioid receptors using the procedure, cell membranes and ligands as described above, with results as listed in Table 13. The values listed below correspond to IC_{50} measurements, unless followed with the notation "Ki" which denotes that for the listed value is a Ki measurement. (Note that for the compounds which were tested more than once, the value listed in Table 13 is the calculated mean.)

Table 13

ID#	Delta IC_{50} (µM)	Kappa IC_{50} (µM)	Mu IC_{50} (µM)
1	>10	0.13	0.62
2	>10	0.19	1.20
3	9.16	0.44	4.05
4	>10	0.11	0.16
5	>10	0.12	0.78
6	>10	0.23	0.42
7	7.11	0.13	1.38

8		0.05	0.83
9		1.40	0.94
10		0.08	0.85
11		0.29	0.82
12		0.20	0.52
13		0.12	0.62
14		0.40	1.20
15		0.33	0.85
16		0.55	1.12
17	>10	0.25	0.65
18	>10	0.28	0.45
19		0.09	0.59
20	>10	0.44	1.28
21	>10	0.32	0.80
22		0.30	0.60
23		0.49	9.20
24	>10	0.75	1.25
25		0.45	1.10
26		0.29	0.79
27		0.03	0.40
28	>10	0.18	0.41
29		0.41	5.41
30	>10	0.71	2.73
31		0.28	2.93
32	>10	0.27	0.45
33		1.16	>10
34		0.27	0.68
35	>10	0.66	0.82
36	1.76	0.23	1.76
38	>10	0.20	0.99
39	>10	3.25	8.83
40	>10	0.40	1.22
41	>10	0.25	2.10
42		0.26	0.54
43		0.32	0.54
44		0.16	1.13
45	1.18	0.10	0.51
46	9.87	0.19	1.32
47	>10	0.09	0.21
48	>10	0.17	0.54
49			0.08
50			1.04
51			0.18
52	4.41	0.05	0.29
53	4.74	0.03	0.07
54	>10	0.11	0.35
55	3.90	0.37	0.60

56	1.25	0.50	0.08
57			0.07
58			1.12
59			0.10
60			0.35
61	0.64	0.08	0.32
62	0.90	0.10	0.06
63	8.78	0.23	3.43
64	7.34	0.24	1.19
65		0.51	0.58
66	5.93	0.13	0.55
67	>10	0.04	0.71
68	>10	0.02	0.26
69	>10	0.04	0.51
70			0.63
71			0.57
72		0.79	1.84
73	>10	0.25	0.68
74	8.02	0.09	0.89
75	>10	0.30	0.98
76	>10	0.02	0.51
78			0.82
79		1.04	3.11
100	>10	0.28	0.23
101	3.93	0.78	0.076
102			0.18
103			0.02
104	0.52	0.08	0.02
105			2.26
106			0.016
107			0.003
108			0.54
115			0.012
116			0.022
117			0.036
124			0.023
127			0.029
129			0.029
130			0.061
131			0.051
132			0.043
133			0.087
137			0.100
138			0.066
139			0.103
140			0.074
142			0.104

143			0.048
144			0.049
145			0.104
146			0.038
147			0.044
148			0.037
149			0.057
152			0.044
153			0.057
155			0.050
156			0.016
158			0.066
159			0.068
160			0.021
161			0.049
164			0.082
165			0.011
166			0.022
167			0.053
168			0.010
169			0.057
171			0.037
173			0.038
174			0.022
175			0.030
176			0.055
177			0.047
178			0.018
179			0.020
180			0.045
181			0.034
183			0.047
192	2.51	0.01	
203	3.08	0.02	0.04
228			0.070
229			0.060
230			0.152
250	>10	0.38	1.20
251	>10	0.45	1.58
252	>10	1.34	3.70
253	2.16	0.40	0.76
254	>10	0.80	2.83
255	>10	0.62	2.49
256	>10	1.18	5.45
257	>10	0.38	0.88
259			0.50
261	>10	0.27	1.56

262			0.85
263			0.59
267			0.77
268			0.95
269			2.49
270			0.41
271	>10	0.07	0.37
275	5.01	0.09	0.45
276	>10	0.70	0.86
280		1.08	2.52
281		0.96	0.58
282		0.77	0.324
283		1.15	3.24
284		0.42	3.20
285		2.69	4.78
289		0.19	1.39
290			0.93
291		0.57	4.56
298	6.06	0.05	0.38
299	>10	1.98	0.43
300	4.84	0.13	0.51
305	8.27	0.171	0.592
307		0.21	0.75
308		0.05	0.20
309		0.09	0.04
310		1.63	1.09
311	1.70	0.28	0.27
312		0.33	0.32
313		0.50	0.33
314		0.16	0.13
315		0.28	0.30
316		0.19	0.49
317		0.22	0.92
318		0.08	0.23
319		0.58	0.32
320		0.12	0.34
321		0.15	0.16
322		0.22	0.13
323		0.10	0.72
324		0.23	0.11
325		0.21	0.73
326		0.01	0.25
327	>10	0.11	0.13
328		0.30	1.03
330	>10	0.48	0.19
331		0.12	0.46
332		0.02	0.08

333		0.39	0.24
334		0.03	0.06
335		0.07	0.13
336		0.04	0.06
337		0.25	0.55
338		0.14	0.74
339	>10	0.18	0.21
340	7.34	0.495	1.29
341	>10	0.29	0.81
342	>10	0.29	0.35
343	2.70	0.42	0.55
344	4.81	0.23	0.55
345	9.27	0.668	0.37
346	1.10	0.14	0.17
347	9.13	0.62	5.4
348	>10	0.93	5.42
349	>10	0.38	1.4
350	3.16	0.078	0.25
351	8.00	0.081	0.38
352	>10	0.27	0.94
353	8.89	0.24	0.47
354	>10	0.15	0.30
355	4.15	0.16	0.18
356	>10	0.08	0.63
358	2.46	0.13	0.17
360	2.51	0.03	0.15
362		0.82	0.20
364		0.18	0.21
365		0.79	1.75
366		0.34	0.26
367		0.36	1.86
368		0.43	1.08
370		0.29	0.35
371		0.73	0.57
372		0.26	0.70
373		1.24	0.37
374		0.73	1.96
376		0.14	0.07
377	2.61	0.093	0.16
378		0.20	0.64
379		0.14	0.16
380		0.23	0.07
381		0.10	0.22
382		0.21	0.15
383		0.06	0.54
386		3.69	>10
388		0.23	>10

389		9.84	7.06
390		1.22	1.79
391		2.18	>10
392		1.39	>10
393		1.04	>10
395		>10	1.10
396		0.81	>10
398	>10	0.25	>10
399		0.75	>10
418	>10	>10	>10
419		0.16	0.13
420	>10	0.42	0.41
421		0.13	0.04
422		>10	>10
423	>1	0.59	0.31
424	0.28	0.60	0.28
425		0.82	0.29
426	>10	1.06	2.74
427		1.45	2.37
428		0.75	0.90
429		0.67	0.80
430	>10	0.89	2.47
431		0.58	1.74
432		0.37	1.00
433		0.42	1.26
434		0.88	0.24
435		0.60	0.22
436		0.83	0.25
437		1.40	0.36
438		>10	>10
439		>10	>10
440		>10	>10
441		>10	>10
442		>10	>10
443		1.75	0.17
444		1.71	0.25
445	>10	0.10	0.06
446	4.12	0.13	0.45
447	0.48		0.48
448		0.17	1.14
451		0.77	0.32
452		1.52	0.57
453		0.39	1.70
454		0.12	0.51
455		0.38	5.16
456		>10	>10
457		9.43	>10

458		1.45	>10
459		3.21	>10
460		0.83	0.90
461	>10	0.25	1.03
462	5.62	0.15	0.12
463		1.77	0.17
464		0.34	2.38
465		0.10	0.38
505	>10	>10	>10
506		0.67	0.529
507	>10	0.277	1.29
508		0.874	0.156
509	0.50	0.11	0.02
510	5.77	0.24	0.69
511	3.91	0.42	0.14
512	0.82	0.98	0.086
513		0.46	0.05
514		0.21	0.26
516		0.77	>10
517		0.45	>10
541	9.28	2.14	0.48
542	>10	0.53	0.16
543	>10	0.71	2.09
544	>10	0.379	0.582
546	>10	2.13	1.29
547	>10	>10	>10
548	>10	0.07	0.54
549	>10	4.37	>10
550	2.61	0.09	0.16
551			1.51
552	>10	1.22	0.066
553	>10	0.75	3.4
554	10.0	9.47	>10
555	0.1	0.56	0.10
556	>10	0.438	0.382
564		0.49	0.04
565		0.41	0.03
566		0.98	0.27
567		1.00	0.17
568		0.72	0.11
569		0.29	0.14
570		0.79	0.05
571	0.05	0.20	0.04
572	3.87	9.85	
573	2.09	7.22	
576	1.4	0.185	0.03
578		>10	2.86

579		2.75	0.17
600		0.49	0.04
601		1.77	0.77
602		0.88	0.07
603		1.32	0.08
604		0.79	0.08
605		0.33	2.38
606		0.58	0.09
607		10.0	10.0
608		10.0	10.0
609		10.0	10.0
610		9.02	10.0
611		0.18	0.05
612		0.44	0.28
613		0.51	0.27
614		1.58	0.56
616	> 5 Ki	0.09 Ki	0.20 Ki
617	> 5 Ki	0.02 Ki	0.09 Ki
618	> 5 Ki	0.04 Ki	0.08 Ki
619	> 5 Ki	0.17 Ki	0.14 Ki
620	> 5 Ki	0.19 Ki	0.28 Ki
621	> 5 Ki	0.02 Ki	0.04 Ki
623	> 5 Ki	0.03 Ki	0.14 Ki
624	> 5 Ki	0.006 Ki	0.07 Ki
625	0.35 Ki	0.003 Ki	0.01 Ki
626	1.45 Ki	0.05 Ki	0.05 Ki
627	> 5 Ki	0.01 Ki	0.06 Ki
628	1.43 Ki	0.008 Ki	0.03 Ki
629	> 5 Ki	0.01 Ki	0.07 Ki
633	> 5 Ki	0.04 Ki	0.44 Ki
634	> 5 Ki	0.03 Ki	0.12 Ki
635	> 5 Ki	0.03 Ki	0.13 Ki
636	3.40 Ki	0.01 Ki	0.23 Ki
637	> 5 Ki	0.08 Ki	0.10 Ki
638	> 5 Ki	0.07 Ki	0.40 Ki
639	1.60 Ki	0.03 Ki	0.01 Ki
640	> 5 Ki	0.21 Ki	0.12 Ki
641	1.58 Ki	0.02 Ki	0.01 Ki
642	3.06 Ki	0.08 Ki	0.02 Ki
643	4.42 Ki	0.04 Ki	0.01 Ki
644	2.28 Ki	0.03 Ki	0.03 Ki
647	> 5 Ki	0.02 Ki	0.05 Ki
648	> 5 Ki	2.87 Ki	5.00 Ki
649	> 5 Ki	0.68 Ki	0.89 Ki
650	> 5 Ki	0.46 Ki	0.74 Ki
651	> 5 Ki	0.31 Ki	0.67 Ki
652	> 5 Ki	0.75 Ki	1.06 Ki

653	> 5 Ki	1.58 Ki	5.00 Ki
654	> 5 Ki	0.06 Ki	0.13 Ki
655	> 5 Ki	0.43 Ki	2.19 Ki
656	> 5 Ki	0.42 Ki	1.52 Ki
657	> 5 Ki	0.04 Ki	0.09 Ki
658	> 5 Ki	0.13 Ki	0.17 Ki
659	> 5 Ki	0.42 Ki	0.13 Ki
660			0.87 Ki
661			0.80 Ki
662			1.60 Ki
663	> 5 Ki	0.018 Ki	0.071 Ki
664	> 5 Ki	0.72 Ki	0.26 Ki
665	> 5 Ki	0.29 Ki	2.71 Ki
666	> 5 Ki	0.14 Ki	2.59 Ki
667	4.14 Ki	0.45 Ki	0.77 Ki
668		1.25	0.19
669		1.36	0.13
670		10.00	10.00
671		10.00	10.00
672		10.00	10.00
673		10.00	10.00
674		10.00	10.00
675	3.10 Ki	0.01 Ki	0.04 Ki
677	0.53 Ki	0.10 Ki	0.08 Ki
678	5.0 Ki	0.04 Ki	0.14 Ki
679	1.52 Ki	0.03 Ki	0.05 Ki
680	> 5 Ki	0.66 Ki	3.02 Ki
681	> 5 Ki	0.58 Ki	0.71 Ki
682		10.00	10.00
683		10.00	10.00
684		5.90	10.00
685		10.00	10.00
686		2.52	10.00
687	0.51 Ki	0.01 Ki	0.01 Ki
688	> 5 Ki	0.16 Ki	0.11 Ki
689	1.46 Ki	0.005 Ki	0.01 Ki
690	1.07 Ki	0.004 Ki	0.03 Ki
691		0.25	0.03
692	3.36 Ki	0.06 Ki	0.02 Ki
693		0.03	0.17
694		0.01	0.85
695		0.16	0.18
696		0.05	0.04
697		0.16	0.20
698		0.19	0.17
699		0.07	0.19
700		0.03	0.92

701		0.05	0.20
702		0.41	0.30
703		0.45	0.11
704	> 5 Ki	0.34 Ki	1.33 Ki
705	> 5 Ki	0.71 Ki	1.50 Ki
706			0.48 Ki
707			0.55 Ki
708			0.49 Ki
709			0.89 Ki
710	> 5 Ki	0.36 Ki	1.09 Ki
711			0.82 Ki
712			1.95 Ki
713			0.23 Ki
714	> 5 Ki		0.59 Ki
715	> 5 Ki	0.15 Ki	0.56 Ki
716	> 5 Ki	0.47 Ki	1.31 Ki
717	> 5 Ki	0.33 Ki	1.32 Ki
718	> 5 Ki	0.03 Ki	0.48 Ki
719	> 5 Ki	0.17 Ki	0.64 Ki
720	> 5 Ki	0.16 Ki	0.57 Ki
721	> 5 Ki	0.17 Ki	0.59 Ki
722		0.44	0.48
723		0.83	0.08
726	0.53 Ki	0.005 Ki	0.04 Ki
727	> 5 Ki	0.21 Ki	0.12 Ki
728	> 5 Ki	0.14 Ki	0.08 Ki
729	0.35 Ki	0.01 Ki	0.003 Ki
733	> 5 Ki	0.07 Ki	0.08 Ki
734	> 5 Ki	1.93 Ki	> 5 Ki

Example 69

In Vitro Assay - Filtration Binding Assay, Dopamine.

The assay was used to measure the binding of representative compounds to D2 receptor, with appropriate selection and substitution of cell membrane and radiolabeled ligand. The following cell membranes and ligands were used for the determination of binding to the respective D2 receptor.

Dopamine: 0.4 µg/well of membrane from cos-7 cell which has been transfected with cloned human Dopamine, Spiperone-I125 ligand at 150 pM final

Both membrane and ligand were diluted such that a 25 µl addition delivered the necessary amount per well, as noted above. Both membrane and ligand were diluted in TNE buffer. The TNE buffer was a mixture of 50mM Tris-HCl pH=7.4, 5mM EDTA and 50mM NaCl. Each test compound was diluted to a concentration from10 µM to 1 pM with 100% DMSO. To each well of a 96 well plate was added 140 µL of TNE buffer, 10 µL of the diluted test compound in DMSO, 25µL of spiperone and 25µL of membrane.

The plate was incubated on a rotating shaker for 1 hour at room temperature. The plate was filtered over GF/C Filterplates, prewetted in 0.03% polyethleneimine, in Filtermate 196 apparatus (Packard). The plate was then washed 6 times with ORL-1 buffer in the filtration apparatus and dried in vacuum oven for 1 hour at a temperature of 50°C.

To each well was then added 25µL Microscint 20 (Packard) (to solubilize bound radioactivity) and each well counted in a Packard TopCount for 1 minute/well using counting parameters optimized for the particular radioligand / opioid receptor being tested. Percent radioactive ligand bound in each reaction was calculated relative to a control using DMSO for maximum binding (no inhibition). Curves were fitted and Ki determined using Graphpad Prizm software (v3.0).

Representative compounds of the present invention were tested according to the procedure outlined above with results as listed in Table 14.

Table 14

ID #	IC_{50} (nM)
422	2208
424	278.2
426	>10,000
430	>10,000
433	3520
439	2334
440	1517
442	3229
327	387.5

Example 70

Elevated Plus Maze (EPM) and Spontaneous Locomotor Activity (SMA)

(Pellow, S., Chopin, P., File. S.E. and Briley, M., *J Neurosci Methods,* (1985) **14,** 149-167)

The procedure used in the EPM was based on the natural aversion of rodents to explore brightly illuminated open and high places, as well as their innate tendency for thigmotaxis. When rats are placed on the elevated-plus maze, they have a normal tendency to remain in the enclosed arms of the maze and avoid venturing into the open arms. Animals treated with typical or atypical anxiolytics show an increase in the percentage of time spent (%Time) and/or the percentage of entries made (%Entries) into the open arms.

The spontaneous locomotor activity test (SMA) was an automated procedure for measuring the effect of a test compound on spontaneous motor activity in an open-field. A drug-induced decrease in spontaneous horizontal or vertical motor activity is regarded as an indication of sedation.

Animals

Male Long-Evans Hooded rats weighing 180 to 200 grams were purchased from Charles River Inc (Portage MI). The rats were housed in groups of four at an ambient temperature of 21 to 23°C in a room with an automated 12/12 hour light/dark cycle, and access to water and a commercial rodent food ad libitum.

EPM Test Apparatus

Each black plastic maze had two open arms and two arms with 40 cm high walls (enclosed arms) of equal 50 cm length extending from the center at right angles, such that arms of similar type are opposite each other. Each plus-maze was elevated approximately 60 cm above the floor. Infrared photo-beams that cross the entrance of each arm and the center of the maze detected the exploratory activity of an animal in the maze. Rats were divided into groups (N=8 to 12) and test compound or vehicle was administered either orally (p.o.) by gavage in a dose volume equivalent to 5 mL/kg or intraperitoneally (i.p.) in a dose volume of 1 mL/kg. One hour after dosing (for

p.o. administration) or 30 minutes after dosing (for i.p. administration), rats were placed on an open arm of the plus-maze facing the center. The 10 minute test was initiated when the rat enters the center of the apparatus. Data collection was automated.

SMA Test Apparatus

The test apparatus consisted of a plastic cubicle (42.0 cm in length; 42.0 cm in width and 30.5 cm height) that was placed in the center of a main frame. Photocell sensors (16 beams from front to back and 16 beams from side to side) were built into the sides of the frame for monitoring horizontal movement. The photocells were located at right angles to each other, projecting horizontal infrared beams of light 2.5 cm apart and 3 cm above the floor to measure horizontal activity, and 2.5 cm apart and 14 cm above the floor to measure vertical activity. Rats were divided into groups (N = 8 to 12). Test compound or vehicle was administered either orally (p.o.) by gavage in a dose volume equivalent to 5 mL/kg or intraperitoneally (i.p.) in a dose volume of 1 mL/kg. At 50 minutes after p.o. administration or at 20 minutes after i.p. administration, each rat was placed into a separate plastic cubicle, and spontaneous exploratory activity was recorded for 10 minutes. Horizontal activity and vertical movements of the rats were recorded by counting the number of times the beams of light were interrupted (horizontal and vertical counts). Collection of the data and preliminary data analysis was automated.

Combined SMA/EPM Test Procedure

All animals were tested in the SMA 50 minutes after drug administration, for a 10 minute test session. Upon completion of the SMA test, the same animals were immediately placed on the EPM for a 10 minute test session.

Test Compounds

The test compound was dissolved in polyethylene glycol, molecular weight 200 (PEG-200) for i.p. administration. Test compound was suspended in an aqueous vehicle (MC) comprised of 0.5% Methylcellulose for p.o. administration.

Derivation and Analysis of EPM Data

Anxiolytic activity of a test compound in the EPM was quantified using two parameters. The percent of total time spent by a rat in one of the two open arms of the apparatus (% open arm time) was calculated as 100 X (time on open arms) / (total time of test session)

The number of times a rat entered the open arms relative to the total entries into all arms and the center area (% open arm entries) was calculated as 100 X (entries into open arms)/(entries into open and closed arms, plus center)

A test compound was considered active in rats whose % open arm time or % open arm entries was significantly greater than in rats that received vehicle. Data was analyzed for statistical significance between drug and vehicle-treated groups via one tailed Mann-Whitney T-Test. If the probability was less than 5% ($p<0.05$) that an increase in the % open arm time and/or % open arm entries in the drug-treated group compared to the vehicle-treated group was due to chance, then the dose of the test compound was considered active.

The total number of entries into all arms and the center of the EPM was recorded as part of the automated data collection in this test. This information (total entries) served as a measure of spontaneous motor activity on the EPM. Compounds with sedative activity reduced the total number of entries in the EPM test. A test compound was considered to have sedative activity in rats whose total entries were significantly less than in rats that received vehicle. Data was analyzed for statistical significance between drug and vehicle-treated groups via one tailed Mann-Whitney T-Test. If the probability was less than 5% ($p<0.05$) that a decrease in the total entries in the drug-treated group compared to the vehicle-treated group was due to chance, then the dose of the

test compound was considered to be a dose at which the compound produces sedation.

Derivation and Analysis of SMA Data

A test compound was considered sedative in rats whose horizontal activity (HA) or vertical movements (VM, rearing) counts were significantly less than that in vehicle-treated rats. HA data was analyzed for statistical significance between drug and vehicle-treated groups that were administered either the vehicle or each dose of the test compound by a one-way analysis of variance. Then Dunnett's multiple comparison method was used to test for a reduction ($p<0.05$, 1-tailed) in the average number of HA counts or VM counts in drug-treated groups, compared to a concurrently run vehicle-treated group. If the probability was less than 5% ($p<0.05$) that a decrease in HA and/or VM in the drug-treated group compared to a concurrently run vehicle-treated group was due to chance, then the dose of the test compound was considered to have sedative activity. Mann-Whitney T-Test was used in cases where the distribution of the data was non-gaussian.

Representative compounds of the present invention were tested according to the EPM and SMA procedures described above, with results as listed in Table 15–19, below. Statistical significance ($P<0.05$) was determined using a Mann-Whitney U Test (one-tailed); NS indicates results were not statistically significant.

Table 15 – EPM and SMA Assay Results

Acute (30 min) Intraperitoneal Administration Compound #64 (*)

Dosage mg/kg, i.p. (# Animals)	Statistics	% Open Arm Time (EPM)	% Open Arm Entries (EPM)	Total Entries (EPM)	Horizontal Activity (SMA)	Vertical Movement (SMA)
Vehicle (PEG-200) (40)	**Mean**	8.92	5.50	94.8	3210	50.0
	S.E.M.	±1.65	±0.86	±4.11	±158	±2.82
	% Change	0.0%	0.0%	0.0%	0.0%	0.0%

0.03 Mg/Kg (28)	**Mean**	9.21	5.92	95.7	3259	49.8
	S.E.M.	±2.14	±1.17	±2.73	±169	±2.37
	% Change	3.2%	7.6%	0.95%	1.5%	-0.4%
	P-value	NS	NS	NS	NS	NS
0.1 Mg/Kg (32)	**Mean**	15.3	10.6	95.4	3845	55.7
	S.E.M.	±1.97	±1.17	±3.91	±200	±2.72
	% Change	71.5%	92.7%	0.63%	19.8%	11.4%
	P-value	0.0053	0.0004	NS	0.0091	NS
0.3 Mg/Kg (32)	**Mean**	13.7	7.86	99.7	3561	58.0
	S.E.M.	±1.96	±0.87	±3.60	±181	±2.69
	% Change	53.6%	42.9%	5.2%	10.9%	16.0%
	P-value	0.0159	0.0146	NS	NS	0.0270
1 Mg/Kg (32)	**Mean**	14.0	7.78	94.8	3611	53.8
	S.E.M.	±2.11	±0.89	±3.73	±184	±1.83
	% Change	57.0%	41.4%	0.0%	12.5%	7.6%
	P-value	0.0155	0.0099	NS	NS	NS
3 Mg/Kg (28)	**Mean**	11.2	7.38	90.8	3449	51.1
	S.E.M.	±1.86	±1.00	±3.90	±172	±2.14
	% Change	25.6%	34.2%	-4.2%	7.4%	2.2%
	P-value	NS	NS	NS	NS	NS
10 Mg/Kg (8)	**Mean**	11.8	7.36	86.8	2803	46.9
	S.E.M.	±4.03	±1.85	±6.91	±165	±3.72
	% Change	32.3%	38.8%	-8.4%	-12.7%	-6.2%
	P-value	NS	NS	NS	NS	NS

(*) Compound #64 was also tested in the SMA and EPM assays, using oral administration, but found to be inactive.

Table 16 – EPM and SMA Assay Results

Acute (1 hr) Oral Administration - Mixture 3 Parts Compound #422 (*): 1 Part Compound #438

Dosage mg/kg, p.o. (# Animals)	Statistics	% Open Arm Time (EPM)	% Open Arm Entries (EPM)	Total Entries (EPM)	Horizontal Activity (SMA)	Vertical Movement (SMA)
Vehicle (0.5% Methylcellulose) (80)	**Mean**	9.61	6.59	102.0	3085	50.7
	S.E.M.	±1.04	±0.59	±3.02	±129	±1.27
	% Change	0.0%	0.0%	0.0%	0.0%	0.0%
0.03 Mg/Kg (16)	**Mean**	7.80	5.53	88.3	3307	53.6
	S.E.M.	±1.82	±1.00	±5.25	±240	±2.41
	% Change	-18.8%	-16.1%	13.4%	7.2%	5.7%
	P-value	NS	NS	0.0235	NS	NS

0.1 Mg/Kg (32)	**Mean**	11.5	7.73	101	3467	59.4
	S.E.M.	±1.97	±1.04	±3.56	±165	±2.50
	% Change	19.7%	17.3%	-1.0%	12.4%	17.2%
	P-value	NS	NS	NS	0.0077	0.0011
0.3 Mg/Kg (56)	**Mean**	12.1	7.85	98.7	3397	53.7
	S.E.M.	±1.38	±0.64	±2.26	±150	±1.68
	% Change	25.9%	19.1%	-3.2%	10.1%	5.9%
	P-value	NS	0.0444	NS	0.0227	0.0408
1 Mg/Kg (48)	**Mean**	14.0	9.55	99.7	3645	55.7
	S.E.M.	±1.68	±0.75	±3.34	±164	±1.83
	% Change	45.7%	44.9%	-2.3%	18.2%	9.9%
	P-value	0.0082	0.0009	NS	0.0015	0.0180
3 Mg/Kg (48)	**Mean**	14.0	8.88	102.0	3621	55.0
	S.E.M.	±1.44	±0.70	±2.23	±188	±1.81
	% Change	45.7%	34.7%	0.0%	17.4%	8.5%
	P-value	0.0032	0.0043	NS	0.0051	0.0338
10 Mg/Kg (56)	**Mean**	17.0	10.3	97.6	3207	51.5
	S.E.M.	±1.51	±0.77	±3.06	±124	±1.51
	% Change	76.9%	56.3%	-4.3%	4.0%	1.6%
	P-value	P<0.0001	P<0.0001	NS	NS	NS
30 Mg/Kg (24)	**Mean**	10.6	8.90	80.7	2741	46.3
	S.E.M.	±1.55	±1.16	±4.20	±171	±2.39
	% Change	10.3%	35.1%	-20.9%	-11.2%	-8.7%
	P-value	NS	0.0197	P<0.0001	NS	0.0091

(*) Compound #422 was also tested in the SMA and EPM assays, using oral administration, but was found to be inactive.

Table 17 – EPM and SMA Assay Results

Acute (1 hr) Oral Administration Compound #424 (†)

Dosage mg/kg, p.o. (# Animals)	Statistics	% Open Arm Time (EPM)	% Open Arm Entries (EPM)	Total Entries (EPM)	Horizontal Activity (SMA)	Vertical Movement (SMA)
Vehicle (0.5% Methyl-cellulose) (24)	**Mean**	5.76	5.48	96.7	2881	49.1
	S.E.M.	±1.50	±1.21	±4.65	±208	±3.28
	% Change	0.0%	0.0%	0.0%	0.0%	0.0%
0.3 Mg/Kg (24)	**Mean**	9.80	7.33	90.0	3033	54.6
	S.E.M.	±2.09	±1.09	±4.90	±232	±3.11
	% Change	70.1%	33.8%	-6.9%	5.3%	11.2%
	P-value	0.0206	NS	NS	NS	NS
1 Mg/Kg (24)	**Mean**	9.76	7.49	91.5	2752	50.3
	S.E.M.	±1.83	±1.28	±3.11	±188	±3.65
	% Change	69.4%	36.7%	-5.3%	-4.5%	2.4%
	P-value	NS	NS	NS	NS	NS

3 Mg/Kg (24)	**Mean**	10.1	7.92	96.3	3300	56.8
	S.E.M.	±1.83	±1.15	±3.43	±145	±2.35
	% Change	75.3%	44.5%	-0.4%	14.5%	15.7%
	P-value	0.0426	0.0398	NS	0.0239	NS
10 Mg/Kg (24)	**Mean**	7.54	7.49	102.6	2588	44.2
	S.E.M.	±1.75	±1.32	±4.63	±215	±3.32
	% Change	30.9%	36.7%	6.1%	-10.2%	-10.1%
	P-value	NS	NS	NS	NS	NS

(†) Compound #424 was also tested in the SMA and EPM assays, using intraperotineal administration, with the following results.

In the rat EPM, at doses of 0.1 mg/kg, 0.3 mg/kg and 3.0 mg/kg, Compound #424 produced significant increases in percent open arm time ($P<0.04$;) with peak activity occuring at doses 0.1 mg/kg and 3 mg/kg (97.5 % increase as compared to vehicle). At doses of 0.1 mg/kg, 0.3 mg/kg, 3.0 mg/kg, and 10.0 mg/kg Compound #424 also produced significant increases in percent open arm entries ($P<0.03$) with peak activity occuring at 3.0 mg/kg and 10.0 mg/kg doses (205% and 237% increase as compared to from vehicle, respectively). Compound #424 significantly reduced the total number of entries into various zones of the maze at doses 1.0 mg/kg, 3.0 mg/kg and 10.0 mg/kg (18.6%, 60.3%, and 76.7% reductions, respectively).

In the rat SMA, at doses of 3.0 mg/kg and 10.0 mg/kg, Compound #424 produced significant reductions (55% and 83.7% reductions, respectively) in horizontal activity ($P<0.001$; Dunnett's multiple comparison test). At doses of 1.0 mg/kg, 3.0 mg/kg and 10.0 mg/kg (17.8%, 73.4%, 93.9% reductions, respectively) Compound #424 produced significant reductions ($P<0.05$; Dunnett's multiple comparison test) in the number of vertical movements (rearing behavior).

Table 18 – EPM and SMA Assay Results

Acute (1hr) Oral Administration of Compound #438

Dosage mg/kg, p.o. (# Aminals)	Statistics	% Open Arm Time (EPM)	% Open Arm Entries (EPM)	Total Entries (EPM)	Horizontal Activity (SMA)	Vertical Movement (SMA)

Vehicle 0.5% Methyl-cellulose (40)	**Mean** **S.E.M.** **% Change**	8.21 ±1.18 0.0%	5.78 ±0.532 0.0%	101.0 ±3.81 0.0%	3244 ±168 0.0%	48.7 ±1.85 0.0%
0.03 Mg/Kg (24)	**Mean** **S.E.M.** **% Change** **P-value**	6.67 ±1.59 -18.8% NS	5.14 ±0.984 -11.1% NS	102.0 ±3.67 1.0% NS	3565 ±216 9.9% NS	54.8 ±2.75 12.5% NS
0.1 Mg/Kg (24)	**Mean** **S.E.M.** **% Change** **P-value**	12.1 ±1.92 47.4% 0.0434	7.77 ±0.913 34.4% 0.0352	103 ±3.81 2.0% NS	3435 ±160 5.9% NS	53.1 ±2.25 9.0% NS
0.3 Mg/Kg (24)	**Mean** **S.E.M.** **% Change** **P-value**	13.8 ±1.56 68.1% 0.0038	8.95 ±0.891 54.8% 0.0010	99.8 ±3.64 -1.2% NS	3450 ±155 6.4% NS	51.7 ±2.36 6.2% NS
1 Mg/Kg (24)	**Mean** **S.E.M.** **% Change** **P-value**	14.8 ±2.13 80.3% 0.0053	9.95 ±1.23 72.1% 0.0025	103.0 ±4.08 2.0% NS	3772 ±170 16.3% NS	56.6 ±2.32 16.2% NS
3 Mg/Kg (24)	**Mean** **S.E.M.** **% Change** **P-value**	12.4 ±1.73 51.0% 0.0170	8.34 ±1.02 44.3% 0.0336	101.0 ±4.75 0.0% NS	3502 ±223 8.0% NS	55.3 ±2.17 13.6% NS
10 Mg/Kg (24)	**Mean** **S.E.M.** **% Change** **P-value**	8.14 ±1.30 0.9% 0.3644	6.42 ±0.856 11.1% NS	94.5 ±3.41 -6.4% NS	3115 ±168 -4.0% NS	54.5 ±1.73 11.9% NS
30 Mg/Kg (7/8)	**Mean** **S.E.M.** **% Change** **P-value**	3.21 ±1.76 -60.9% 0.0486	6.65 ±2.28 15.1% NS	86.3 ±6.40 -14.6% NS	2730 ±185 -15.8% NS	45.3 ±3.34 -7.0% NS

Table 19 – EPM and SMA Assay Results

Sub-Chroinc (8-day/once a day) Oral Administration Compound #438

Dosage mg/kg, p.o. # Animals	Statistics	**% Open Arm Time (EPM)**	**% Open Arm Entries (EPM)**	**Total Entries (EPM)**	**Horizontal Activity (SMA)**	**Vertical Movement (SMA)**
Vehicle (0.5% methyl-cellulose) (16)	Mean S.E.M. % Change	7.96 ±1.87 0.0%	6.53 ±1.05 0.0%	101.0 ±4.72 0.0%	3451 ±196 0.0%	54.6 ±3.35 0.0%

0.1 Mg/Kg (16)	Mean S.E.M. % Change P-value	17.2 ±1.84 116.1% 0.0012	9.17 ±0.931 40.4% 0.0338	102 ±4.82 1.0% NS	3813 ±170 10.5% NS	62.9 ±1.75 15.2% NS
0.3 Mg/Kg (16)	Mean S.E.M. % Change P-value	21.8 ±1.8 173.9% P<0.0001	11.8 ±0.891 80.7% 0.0007	99.1 ±5.56 -1.9% NS	4390 ±253 27.2% P<0.05	61.1 ±3.61 11.9% NS
1 Mg/Kg (16)	Mean S.E.M. % Change P-value	15.1 ±1.96 89.7% 0.0064	9.57 ±1.12 46.6% 0.0007	99.6 ±3.42 -1.4% NS	3979 ±151 15.3% NS	59.5 ±2.53 9.0% NS
3 Mg/Kg (16)	Mean S.E.M. % Change P-value	16.9 ±2.9 112.3% 0.0047	9.0 ±1.21 37.8% 0.0367	106.0 ±4.42 5.0% NS	4253 ±306 23.2% P<0.05	59.9 ±3.47 9.7% NS

Example 71

In Vivo Study - Vogel Rat Conflict Assay

(Vogel, J.R., et al., *Psychopharmacology*, (1971), 21, 1)

This behavioral assay assesses the anxiolytic activity of a test compound by determining the ability of rats to release (disinhibit) behavior that has been suppressed by punishment.

Method

Male adult rats were deprived of water for 48 hours and were deprived of food for 24 hours prior to testing. After the first 24 hours of water deprivation, the rats were placed in the conflict chamber for a training period; during which time the rats were allowed 200 unpunished licks from a bottle containing tap water. The experiment was run the following day. The rats were dosed with the test compound orally by gavage or intraperitoneally (i.p.). At the expected time of peak activity (30 minutes for i.p administration and 60 min for oral administration), the rats were placed in the conflict chamber and were allowed access to tap water. If they failed to drink, the experiment was terminated in 5 min, and the animals were evaluated for signs of CNS depression. The first lick initiated a 3min test session. Subsequently, every 20th lick was punished with an 0.2 sec, 0.6 milliampere (RMS) shock delivered via the stainless steel drinking

tube. Vehicle treated control animals were generally willing to accept a median of 3 to 8 shocks per test session. Animals treated with an active anxiolytic drug tolerated significantly more shocks than control animals. The Wilcoxon rank-sum test (Mann-Whitney U-test) was used to test for an increase ($p<0.05$, 1 tailed) in the median number of shocks in the drug treated group compared with a concurrently run control treated group. The assay was considered to be valid if the effects of a known anxiolytic (a positive control) were detected within the same experiment. A test compound was considered active if there was a significant difference in the median number of shocks tolerated between the drug treated and the control group.

Compound #64 and a mixture of three parts Compound #422 to one part Compound 438 (denoted as "CMPD mix" in the table below) were tested according to the procedure described above, with results as listed in Table 20, below. No. / Group indicates the number of animals tested for the listed dosage. % increase in mean no of shock is as compared with vehicle. Statistically significant results were those with a Mann-Whitney U Test (one tailed) p value of <0.05.

Table 20

	Dose (mg/kg, i.p.)	**No / Group**	**% Increase Mean No. of Shocks**	**P Value**
PEG-200 (Vehicle)	0	25	0	-
Compound #64	0.3	8	-10%	0.3294
Compound #64	1	24	25%	0.3480
Compound #64	3	24	96%	0.0692
Compound #64	10	22	150%	0.0002
Compound #64	30	8	-26%	0.5000
	Dose (mg/kg, p.o.)	**No / Group**	**% Increase Mean No. of Shocks**	**P Value**
0.5% Methylcellulose (Vehicle)	0	17	0	-

CMPD mix	0.3	8	8%	0.3304
CMPD mix	1	8	39%	0.4418
CMPD mix	3	8	47%	0.0425
CMPD mix	10	18	54%	0.1634
CMPD mix	30	12	47%	0.0327

Example 72

Stress Induced Hyperthermia in Vivo Assay

Procedure

Male Long-Evans Hooded rats weighing 180 to 200 grams at the time of purchase were obtained from Charles River Laboratories (Raleigh, North Carolina). Upon arrival, the animals were group housed four per cage in quarantine for 5 days in wire-mesh cages at an ambient temperature of 21 to 23°C with an automated 12/12 hour light/dark cycle and ad libitum access to water and a commercial rodent chow. The rats were then transferred to a general housing room for a one-week acclimation with housing and environmental conditions, and 12/12 hour light/dark cycle conditions. Animals were fasted overnight (18 hours) prior to experiment.

On the day of experiment, group-housed (4/group) Long-Evans Hooded rats were divided into various treatment groups (N = 8 to 32) and test compound at 0.03-3.0 mg/kg or vehicle was administered orally (p.o.) by gavage in a dose volume equivalent to 5 mL/kg. One hour after dosing, baseline rectal temperatures were recorded for each rat. Rats were then immediately isolated in shoebox cages with ALPHA-DRY bedding. Rectal temperatures were then recorded at 15 min, 30 min, and 45 min after isolation (i.e, 1 hr 15 min, 1 hr 30 min, and 1 hr 45 minutes after test compound or vehicle administration). All experiments were conducted during the light cycle. After completion of the behavioral portion of the study, each animal was killed via decapitation using a guillotine and trunk blood was collected in 5 mL vacutainer tube containing EDTA and placed on ice. The samples were then centrifuged at 3800 RPM for 10 minutes and plasma was removed and placed on dry ice in an Eppendorff sample tube. Plasma samples were stored at –

80°C and later used for determining ACTH, corticosterone, and glucose levels. Plasma samples were outsourced to Anilytics, Inc. for determination of plasma levels of ACTH, coricosterone, and glucose. A Mann-Whitney U t-test (one-tailed) was used for statistical analysis of behavioral data and an unpaired t-test (one-tailed) was used for analysis of plasma ACTH, corticosterone, and glucose levels.

Results

Compound #438 was suspended in an aqueous vehicle comprised of 0.5% (w/v) methylcellulose (15 centipoises) solution.

Rats treated with Compound #438 showed an attenuation of rectal temperature in the SIH model as described above, at 0.03 mg/kg, 0.01 mg/kg, 0.3mg/kg, 1.0 mg/kg and 3.0 mg/kg, with measured temperatures and p values as listed in Table 21. In the Table below, the abbreviation "S.E.M." represents the standard error of the mean and the abbreviation "N.S." indicates that the p value indicated that any measured difference in temperature was not statistically significant.

Table 21

Compound (dose)		Temp. °C 0 (Basal)	Temp. °C 15 min	Temp. °C 30 min	Temp. °C 45 min
Vehicle	**Mean**	37.4	38.7	38.9	38.9
	S.E.M.	±0.12	±0.062	±0.053	±0.049
	P-value				
Cmpd #438 (0.03 mg/kg)	**Mean**	37.5	38.7	38.6	38.4
	S.E.M.	±0.166	±0.0707	±0.139	±0.128
	P-value	NS	NS	0.0188	0.0018
Cmpd #438 (0.1 Mg/Kg)	**Mean**	37.2	38.4	38.5	38.5
	S.E.M.	±0.119	±0.093	±0.101	±0.125
	P-value	NS	0.0139	0.0011	0.0098
Cmpd #438 (0.3 Mg/Kg)	**Mean**	37.4	38.4	38.5	38.3
	S.E.M.	±0.121	±0.0873	±0.0782	±0.0853
	P-value	NS	0.0068	<0.0001	<0.0001
Cmpd #438 (1.0 Mg/Kg)	**Mean**	37.1	38.4	38.5	38.2
	S.E.M.	±0.105	±0.108	±0.0856	±0.109
	P-value	0.0280	0.0148	<0.0001	<0.0001
Cmpd #438	**Mean**	37.0	38.2	38.4	38.2

(3.0 Mg/Kg)	**S.E.M.**	±0.0949	±0.146	±0.124	±0.131
	P-value	0.0121	0.0011	0.0002	<0.0001

Plasma stress hormone levels for rats treated with Compound #438 showed a 25 % reduction in plasma ACTH levels at 0.3 mg/kg, the reduction calculated to be statistically significant (P=0.0170). Changes in the plasma levels of corticosterone were not statistically significant.

Example 73

Tissue Distribution Assay

Procedure

Male Long-Evans Hooded rats weighing 180 to 200 grams at the time of purchase were obtained from Charles River Laboratories (Portage, Michigan). Upon arrival, the animals were group housed four per cage in quarantine for 5 days in wire-mesh cages at an ambient temperature of 21 to 23°C with an automated 12/12hour light/dark cycle and ad libitum access to water and a commercial rodent chow. The rats were then transferred to a general housing room for a one-week acclimation with housing and environmental conditions, and 12/12 hour light/dark cycle conditions. Animals were fasted overnight (18 hours) prior to experiment.

On the day of experiment, two Long-Evans Hooded rats were treated orally with a vehicle (0.5% methylcellulose) and eight rats were treated orally with 10.0 mg/kg of Compound #438. Five hours after drug administration, each treated animal was killed via decapitation using a guillotine, trunk blood was collected and the following tissues were harvested for analysis of compound distribution in the following tissues/systems: (1) brain regions including the cortex, cerebellum, hypothalamus and hippocampus, (2) heart, (3) lung, (4) kidney, (5) liver, (6) spleen, (7) adrenal glands, (8) small intestines, (9) large intestines, (10) muscle, as well as (11) whole blood and (12) plasma.

Whole blood and plasma samples were prepared for analysis as follows. 400 µL of acetonitrile containing 1 µM internal standard (propranolol) was

added to 200 μL of plasma or whole blood to precipitate proteins. Samples were centrifuged at 5000 g for 5 minutes and supernatant removed for analysis by LC-MS. 400 μL of water was added to adjust sample solvent strength and prevent peak splitting. Calibration standards were prepared by adding appropriate volumes of stock solution directly into plasma and treated identically to collected plasma samples. LC-MS analysis was performed using MRM for detection of characteristic ions for each test compound and internal standard.

Tissue samples were prepared for analysis as follows. Individual tissue samples were extracted with 2 mLs of ethanol if the tissue weight was 1 gram or less. A volume of ethanol in milliliters equal to twice the weight in grams was added if the tissue weight was greater than 1 gram. The extracts were centrifuged to precipitate solids and the supernatant was transferred to clean Eppendorf tubes. 200 μL of this was transferred to autosampler vials and 20μL of acetonitrile containing 1 μM internal standard (propranolol) was added for analysis by LC/MS. Calibration standards were prepared using an equivalent volume of tissue extract at 2 ml per gram from undosed or vehicle dosed animals. The extracts from brain tissue were concentrated in order to achieve lower detection limits(<1nM). For these, 20μL of 1uM propranolol in acetonitrile was added to 700μL of extract and blown to dryness under nitrogen. These were then reconstituted in 100μL of 1:1::acetonitrile:water and analyzed by LC/MS. Calibration standards were prepared in blank extract and treated exactly as samples.

Measured values within the various samples were as listed in Table 22 and 23, for vehicle and Compound #438 treated rats, respectively. Results are reported in μmoles/kg or ng/g as appropriate converting the sample concentrations based on extraction solvent/tissue ratio. These units are on the same scale as μmoles/l or ng/ml as typically reported for plasma and can be used for comparison. Detection of analytes down to 0.005 μmoles/kg were typical for the LC-MS used.

Table 22 – Vehicle (Control)

	Animal 9 (Vehicle)		Animal 10 (Vehicle)	
	µM	µM/kg	µM	µM/kg
Cortex	0.000	0.000	0.000	0.000
Cerebellum	0.000	0.000	0.000	0.000
Hypothalamus	0.000	0.000	0.000	0.000
Hippocampus	0.000	0.000	0.000	0.000
Heart	0.000	0.000	0.000	0.000
Lung	0.000	0.000	0.000	0.000
Liver	0.000	0.000	0.000	0.000
Spleen	0.000	0.000	0.000	0.000
Kidney	0.000	0.000	0.000	0.000
Adrenal Glands	0.000	0.000	0.000	0.000
Lr intestine	0.000	0.000	0.000	0.000
Sm Intestine	0.011	0.027	0.000	0.000
Muscle	0.000	0.000	0.000	0.000
Plasma	0.000		0.000	
Whole Blood	0.000		0.000	

Table 23 – Compund #438 Tissue Concentration

	Animal 1		Animal 2		Animal 3	
	µM	µM/kg	µM	µM/kg	µM	µM/kg
Cortex	0.0062	0.030	0.0047	0.020	0.0047	0.030
Cerebellum	0.0402	0.161	0.014	0.090	0.0189	0.140
Hypothalamus	0.0124	0.413	0.0055	0.367	0.0064	0.427
Hippocampus	0.0195	0.650	0.0021	0.070	0.0009	0.030
Heart	2.036	4.072	2.485	5.144	2.346	4.692
Lung	5.821	15.119	4.737	12.632	5.153	13.741
Liver	6.664	13.257	6.409	12.785	4.632	9.294
Spleen	9.140	25.389	7.232	17.857	7.163	23.106
Kidney	3.747	7.546	4.031	8.062	4.123	8.027
Adrenal Glands	0.967	24.175	0.988	28.229	1.289	28.644
Lg intestine	4.518	9.036	12.478	29.019	30.593	59.694
Sm Intestine	21.836	53.916	27.120	84.750	17.359	48.219
Muscle	0.919	1.814	0.688	1.371	0.791	1.560
Plasma	0.419		0.426		0.360	
Whole Blood	0.166		0.147		0.135	
	Animal 4		Animal 5		Animal 6	
	µM	µM/kg	µM	µM/kg	µM	µM/kg
Cortex	0.0026	0.0130	0.0038	0.017	0.0023	0.010
Cerebellum	0.0045	0.0350	0.0026	0.019	0.0101	0.067

Hypothalamus	0.0062	1.2400	0.0030	0.200	0.0036	0.360
Hippocampus	0.0140	0.2550	0.005	0.200	0.002	0.010
Heart	1.664	3.328	1.785	3.471	2.478	4.878
Lung	4.361	11.629	3.533	7.438	5.290	20.346
Liver	3.879	7.758	4.006	7.861	5.090	10.180
Spleen	5.207	13.703	6.730	19.229	7.742	26.697
Kidney	3.841	7.570	3.993	7.791	4.718	9.523
Adrenal Glands	1.088	31.086	1.075	26.875	1.487	59.480
Lr intestine	2.231	6.562	24.916	56.627	9.584	26.622
Sm Intestine	13.898	38.077	16.743	41.858	14.131	56.524
Muscle	0.651	1.280	0.917	1.754	0.977	1.954
Plasma	0.289		0.183		0.174	
Whole Blood	0.088		0.469		0.266	
	Animal 7		**Animal 8**			
	µM	**µM/kg**	**µM**	**µM/kg**		
Cortex	0.0055	0.025	0.0139	0.062		
Cerebellum	0.0138	0.095	0.0102	0.068		
Hypothalamus	0.0101	0.673	0.0027	0.180		
Hippocampus	0.0065	0.217	0.0019	0.190		
Heart	1.572	2.977	2.083	4.261		
Lung	5.655	15.930	6.189	11.902		
Liver	5.887	10.398	5.677	11.120		
Spleen	8.062	29.859	9.205	28.766		
Kidney	4.109	7.645	4.750	8.782		
Adrenal Glands	1.267	42.233	1.946	64.867		
Lr intestine	33.756	68.194	5.070	9.941		
Sm Intestine	25.408	72.594	13.018	39.448		
Muscle	0.882	1.707	1.509	3.006		
Plasma	0.268		0.470			
Whole Blood	0.061		0.093			

Example 74

Oral Formulation

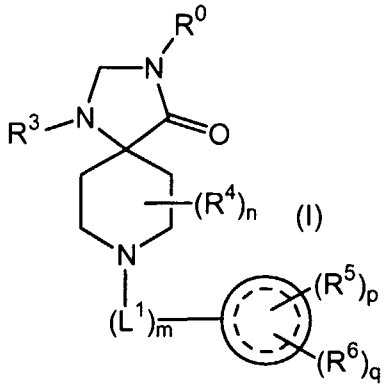
As a specific embodiment of an oral composition, 100 mg of the compound #438 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gel capsule.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual

variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

What is claimed is:

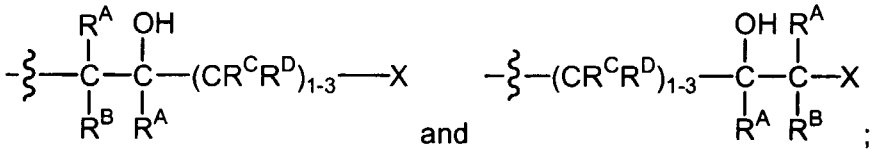
1. A compound of the formula (I)



(I)

wherein

R^0 is selected from the group consisting of



and

;

each R^A and R^B is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

each R^C and R^D is independently selected from the group consisting of hydrogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl; wherein the aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl substituent is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano or $N(R^E)_2$;

each R^E is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-C(O)O-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one or more substituents independently selected from carboxy, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxycarbonyl or $-CONR^1R^2$;

each R^1 and R^2 is independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkoxy, C_{1-8}alkoxycarbonyl, cycloalkyl, cycloalkyl-C_{1-4}alkyl, partially unsaturated carbocylyl, partially unsaturated carbocyclyl-C_{1-4}alkyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkoxy, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, -C(O)-C_{1-6}alkyl, -C(O)-aryl, -C(O)-arC_{1-4}alkyl, -C(O)-heteroaryl, -C(O)-heterocycloalkyl, -C(O)O-cycloalkyl and –C(O)O-aryl, -C(O)O-arC1-4alkyl, -C(O)O-(partially unsaturated carbocyclyl), -C(O)O-heteroaryl, -C(O)O-heterocycloalkyl; wherein the C_{1-8}alkyl, cycloalkyl, partially unsaturated carbocyclyl, aryl, arC_{1-8}alkyl, heteroaryl or heterocycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, -C(O)-C_{1-4}alkyl, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl, $N(R^E)$-C(O)$C(CH_3)_3$, -C_{1-4}alkyl-$N(R^E)$-C(O)O-C_{1-4}alkyl and –$N(R^E)$-C(O)O-C_{1-4}alkyl, aryl, aryloxy, cycloalkyl, heteroaryl, aryl substituted heteroarylaminosulfonyl or C_{1-6}alkylthio;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, hydroxy substituted C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4}alkyl, heteroaryl, heterocycloalkyl, di(C_{1-6})alkylamino-carbonyl, C_{1-4}alkoxycarbonyl-$N(R^E)$- or arylamino-C_{1-4}alkyl; wherein the aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl substituent is optionally further substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, phenyl or substituted phenyl; wherein the substituents on the phenyl are one or more independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

R^3 is selected from the group consisting of aryl, arC_{1-6}alkyl and heteroaryl; wherein the aryl, arC_{1-6}alkyl or heteroaryl group is optionally

substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4}alkyl and hydroxy substituted C_{1-4}alkyl;

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6}alkyl and C_{3-6}alkenyl; wherein the double bond of the C_{3-6}alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6}alkyl or C_{3-6}alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6}alkyl, fluorinated C_{1-6}alkyl or C_{1-6}alkoxy;

 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6}alkyl, hydroxy substituted C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, NR^1R^2, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO-NR^1R^2, -SO_2-NR^1R^2 and -C(O)-NR^1R^2;

q is an integer from 0 to 1;

R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

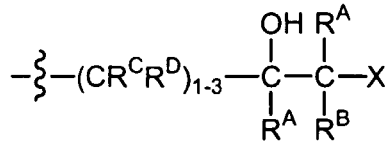
L^2 is selected from the group consisting of -C_{1-6}alkyl-, -C_{2-4}alkenyl-, -C_{2-6}alkynyl-, -O-, -S-, -NH-, -N(C_{1-4}alkyl)-, -C_{1-6}alkyl-O-, -C_{1-6}alkyl-S-, -O-C_{1-6}alkyl-, -S-C_{1-6}alkyl-, -O-C_{2-6}alkyl-O-, -S-C_{2-6}alkyl-S-, -SO_2-, -SO_2NH-, -SO_2N(C_{1-4}alkyl)-, -NH-SO_2-, -N(C_{1-4}alkyl)-SO_2-, -C(O)-O- and -O-C(O)-;

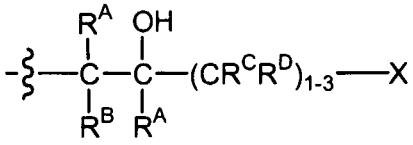
R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano,

$N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.

2. A compound as in Claim 1 wherein

R^0 is selected from the group consisting of 

and 

each R^C and R^D is independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, hydroxy, carboxy or aryl; wherein the aryl is optionally substituted with one to two substituents independently selected from hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano or $N(R^E)_2$;

X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SO-R^1$, $-SO_2-R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-NR^1-C(O)OC(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one to two substituents independently selected from C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxycarbonyl or carboxy;

R^1 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, heteroaryl, heteroaryl-alkyl, heterocycloalkyl, heterocycloalkyl-alkyl, cycloalkyl-alkyl, $C(O)-C_{1-4}$alkyl and -C(O)-heteroaryl;

wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}$alkyl, $N(R^E)-C(O)OC(CH_3)_3$, nitro, trifluoromethyl, trifluoromethoxy, phenyl,

phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C_{1-4}alkylthio;

R^2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, cycloalkyl, cycloalkyl-C_{1-4}alkyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, partially unsaturated carbocyclyl, partically unsaturated carbocyclyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, -C(O)-C_{1-4}alkyl, -C(O)-aryl, -C(O)-arC_{1-4}alkyl, -C(O)-heteroaryl,–C(O)-heterocycloalkyl, -C(O)O-cycloalkyl and –C(OO)-C_{1-4}alkyl;

wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl, partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl, $(CH_3)_3COC(O)$-$N(R^E)$-C_{1-4}-alkyl, nitro, cyano, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl substituted heteroaryl-aminosulfonyl, -C(O)-C_{1-4}alkyl or C_{1-4}alkylthio;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group;

wherein the heteroaryl or heterocycloalkyl is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, hydroxy substituted C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, phenyl, arC_{1-4}alkyl, heterocycloalkyl, di(C_{1-4}alkyl)amino-carbonyl, C_{1-4}alkoxycarbonylamino or phenylamino-C_{1-4}alkyl;

wherein the phenyl or arC_{1-4}alkyl substituent on the heteroaryl or heterocycloalkyl group is optionally substituted with one or two substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$ or substituted phenyl; wherein the substituents on the phenyl are one to three independently selected from halogen;

R^3 is selected from the group consisting of aryl and arC_{1-4}alkyl; wherein the aryl or arC_{1-4}alkyl group is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

n is an integer from 0 to 1;

L^1 is C_{1-4}alkyl; wherein the C_{1-4}alkyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-4}alkyl, fluorinated C_{1-4}alkyl or C_{1-4}alkoxy;

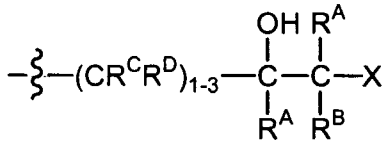
R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO- $N(R^E)_2$, -SO_2- $N(R^E)_2$ and -C(O)- $N(R^E)_2$;

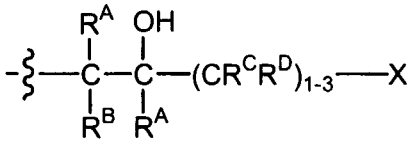
L^2 is selected from the group consisting of -C_{1-4}alkyl-, -O-, -S-, -$N(R^E)$-, -C(O)O- and -O-C(O)-;

R^7 is selected from the group consisting of cycloalkyl, aryl, heteroaryl and heterocycloalkyl; wherein the aryl, heteroaryl or heterocycloalkyl group is optionally substituted with one to two substituents independently selected from hydroxy, carboxy, halogen, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy or C_{1-4}alkoxycarbonyl;

or a pharmaceutically acceptable salt thereof.

3. A compound as in Claim 2 wherein

R^0 is selected from the group consisting of 



and

each R^A, R^B, R^C and R^D is hydrogen;

X is selected from the group consisting of -NR^1R^2, -OR^1, -SR^1, -S-(C_{2-4}alkyl)-NR^1R^2 and -S-(C_{2-4}alkyl)-NR^1-C(O)O-$C(CH_3)_3$; wherein the alkyl portion of the -S-(C_{2-4}alkyl)-NR^1R^2 or -S-(C_{1-4}alkyl)-NR^1-C(O)O-$C(CH_3)_3$ group is optionally substituted with a carboxy or C_{1-4}alkoxycarbonyl group;

R^1 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxycarbonyl, arC_{1-4}alkyl and C(O)-C_{1-4}alkyl;

wherein the C_{1-4}alkyl or aryl group, whether alone or part of a substituent group, is optionally substituted with one to two substituents independently selected from carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$ or $N(R^E)$-C(O)$OC(CH_3)_3$;

R^2 is selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, cycloalkyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkyloxy, partially unsaturated carbocyclyl, partially unsaturated carbocyclyl-C_{1-4}alkyl, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, cycloalkyl-C_{1-4}alkyl, -C(O)arC_{1-4}alkyl, -C(O)-heteroaryl, -C(OO)-cycloalkyl and –C(O)O-C_{1-4}alkyl;

wherein the C_{1-4}alkyl, aryl, arC_{1-4}alkyl, partially unsaturated carbocyclyl, heteroaryl, heterocycloalkyl or cycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one to three substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2$-C_{1-4}alkyl, $(CH_3)_3CO$-C(O)-$N(R^E)$-C_{1-4}alkyl, nitro, trifluoromethyl, trifluoromethoxy, phenyl, phenoxy, heteroaryl, cycloalkyl, 1-phenyl-pyrazol-2-yl-aminosulfonyl or C_{1-4}alkylthio;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from heterocycloalkyl and heteroaryl;

wherein the heteroaryl or heterocycloalkyl is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4}alkyl, hydroxy substituted C_{1-4}alkyl, C_{1-4}alkoxy, phenyl, arC_{1-4}alkyl, heterocycloalkyl, C_{1-4}alkoxycarbonyl, amino, C_{1-4}alkylamino, di(C_{1-4}alkyl)amino, di(C_{1-4}alkyl)amino-carbonyl, t-butoxycarbonylamino or phenylamino-C_{1-4}alkyl;

wherein the phenyl or arC_{1-4}alkyl substituent is optionally substituted with one or two substituents independently selected from chloro, trifluoromethyl or chlorophenyl;

R^3 is aryl; wherein the aryl group is optionally substituted with one or more substituents independently selected from halogen;

n is 0;

L^1 is C_{1-4}alkyl;

R^5 is selected from the group consisting of halogen, C_{1-4}alkyl and trifluoromethyl;

R^6 is $-(L^2)_0-R^7$;

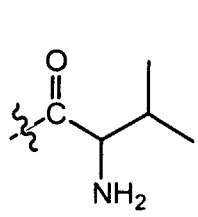
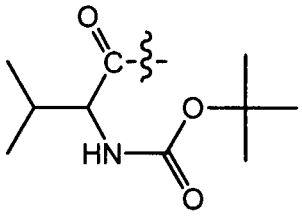
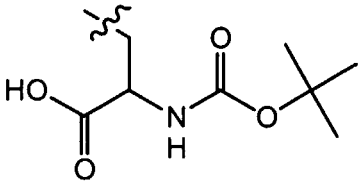
R^7 is selected from the group consisting of aryl and heteroaryl;

or a pharmaceutically acceptable salt thereof.

4. A compound as in Claim 3 wherein

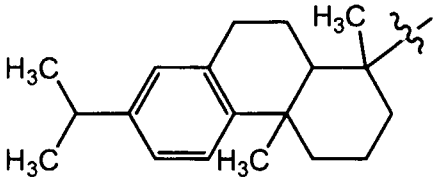
R^0 is selected from the group consisting of $-CH_2-CH(OH)-CH_2-X$ and $-CH_2-CH_2-CH(OH)-CH_2-X$;

X is selected from the group consisting of $-NR^1R^2$, $-OR^1$, $-SR^1$, $-S-CH_2CH(CO_2H)-NH-C(O)-CH_3$ and $-S-CH_2CH(CO_2H)-NH-C(O)O)C(CH_3)_3$;

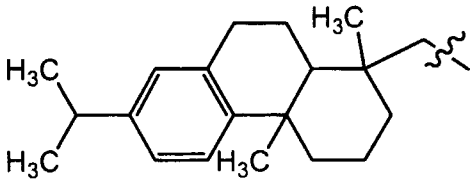
R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, amino-n-propyl, dimethylaminoethyl, benzyl, phenylethyl, 4-methyl-benzyl, , , 2-(3,4-dimethoxy-phenyl)ethyl, 3-methyl-phenyl, ethoxy-carbonyl-methyl, 2-amino-2-methoxycarbonyl-ethyl, t-butoxycarbonyl and ;

R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, carboxy-methyl, ethoxycarbonylmethyl, 2,2,2,-triluoroethyl, ethoxy, dimethylaminoethyl, t-butoxycarbonylamino-ethyl, n-butyl, t-butyl, n-propyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, di(n-butyl)amino-n-propyl, t-butoxycarbonylamino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, t-butoxycarbonyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 3,4-dimethoxyphenyl, 2-aminophenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-cyclohexylphenyl, 4-(aminoethyl)phenyl, 4-(t-butoxycarbonylamino-ethyl)-

phenyl, -CH(CH_3)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl), 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonylbenzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)benzyl, 4-(dimethylamino)benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, (2,5-dimethoxy-2,5-dihydro-fur-2-yl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), 6-methylthio-2-pyridyl-carbonyl, thienyl-methyl, 2-thienylethyl, 4-pyridinyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 1-phenyl-2-(t-butoxycarbonyl)ethyl, -C(O)-C(OCH_3)(CF_3)-phenyl, -C(O)O-(2-isopropyl-5-methyl-cyclohexyl), 1-(4-ethoxycarbonyl-piperidinyl), 2-(3H-imidazol4-yl)ethyl, 2-(1,2,3,4-tetrahydro-isoquinolinyl), 2-furyl-methyl,



,



, 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl, 2-(2-pyridyl)-ethyl, 2-(6-fluoro-2-indolyl)ethyl and 2-phenyl-cyclopropyl;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-morpholinyl, 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-pyrrolidinyl-piperidinyl), 1-(4-phenyl-piperidinyl), 1-(3-hydroxy-piperidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3,5-dimethyl-piperidinyl), 1-(4-dimethylamino-piperidinyl), 1-(4-(3,4-methylenedioxyphenylmethyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-t-butoxycarbonylamino-piperidinyl), 1-(2,3-dihydro-1H-pyrrolyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-pyrrolidinyl, 1-(2,3,-dihydro-pyrrolidinyl), 1-(3-hydroxy-pyrrolidinyl), 1-(3-(S)-hydroxy-pyrrolidinyl), 1-piperidinyl, 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-ethoxycarbonyl-piperidinyl), 1-imidazolyl, 1-(2-(phenylamino-methyl)-N-pyrrolidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(3,4-dihydroxy-2,5-bis-hydrooxymethyl-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-methylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino)-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl);

R^3 is selected from the group consisting of phenyl and 4-fluorophenyl;

L^1 is selected from the group consisting of $-CH_2-$, $-CH(CH_3)-$ and $-CH_2CH_2-$;

 is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl, 2-naphthyl, 1,2,3,4-tetrahydro-naphthyl, 2-thienyl, benzothienyl, 4,5,6,7-tetrahydro-benzothienyl, bicyclo[3.1.1]hepten-2-yl, bicyclo[3.1.1]heptyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl;

R^5 is selected from the group consisting of chloro, methyl, n-propyl and trifluoromethyl;

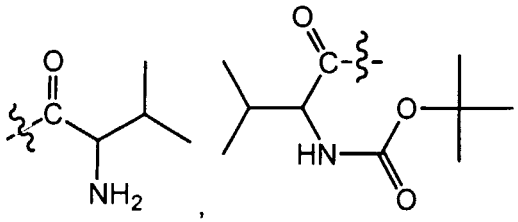
R^7 is selected from the group consisting of phenyl and 2-thienyl;

or a pharmaceutically acceptable salt thereof.

5. A compound as in Claim 4 wherein

X is selected from the group consisting of $-NR^1R^2$, $-SR^1$ and $-S-CH_2CH(CO_2H)-NH-C(O)-CH_3$.

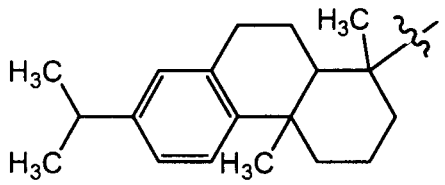
R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, phenylethyl,



, 3-methyl-phenyl, 2-(3,4-dimethoxyphenyl)-ethyl, ethoxycarbonyl-methyl, dimethylamino-ethyl and 2-amino-2-methoxycarbonyl-ethyl;

R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, 2,2,2-triluoroethyl, ethoxy, dimethylaminoethyl, n-butyl, t-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 2-aminophenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, 3,4-dimethoxyphenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 4-carboxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-

difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), thienylmethyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-



methyl, , 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl, 2-phenoxy-ethyl and 2-(6-fluoro-2-indolyl)-ethyl;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-phenyl-piperidinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperiazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-morpholinyl, 1-pyrrolidinyl, 1-(2,3-dihydro-pyrrolidinyl), 1-piperidinyl, 1-(3,5-dimethyl-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-(ethoxycarbonyl)-piperidinyl), 1-imidazolyl and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl);

L^1 is selected from the group consisting of $-CH_2-$ and $-CH_2-CH_2-$;

 is selected from the group consisting of cyclooctyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, cyclohexyl, phenyl, 1-naphthyl and (3a-S)-2,3,3a,4,5,6-hexahydro-1H-phenalen-2-yl;

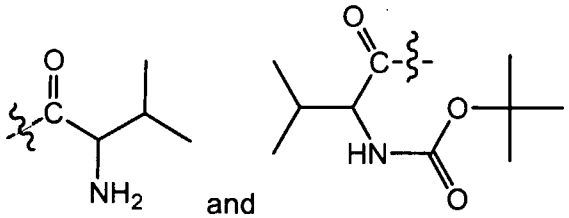
p is an integer from 0 to 2;

R^7 is 2-thienyl;

or a pharmaceutically acceptable salt thereof.

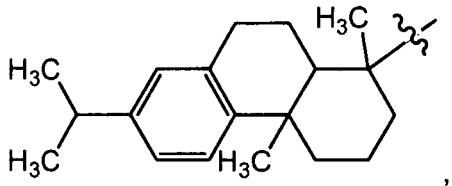
6. A compound as in Claim 5 wherein

R^1 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, n-butyl, t-butyl, dimethylaminoethyl, benzyl, phenylethyl, 2-(3,4-dimethoxyphenyl)-ethyl, dimethylamino-ethyl, ethoxycarbonyl-methyl,

 and ;

R^2 is selected from the group consisting of hydrogen, methyl, methoxy, ethyl, ethoxycarbonyl-methyl, ethoxy, dimethylaminoethyl, n-butyl, n-propyl, di(n-butyl)amino-n-propyl, 3-phenyl-n-propyl, 3-(2-pyridyl)-n-propyl, cyclopropyl, phenyl, 4-fluorophenyl, 4-methylphenyl, 2-aminophenyl, 3,4-dimethoxyphenyl, 4-(t-butoxycarbonylamino-ethyl)-phenyl, 4-biphenyl, 2-ethoxyphenyl, 4-((1-phenyl-pyrazol-2-yl)-aminosulfonyl)-phenyl, 4-(aminoethyl)-phenyl, benzyl, benzyloxy, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-ethoxybenzyl, 3-ethoxybenzyl, 2-bromobenzyl, 3-bromobenzyl, 4-bromobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-iodobenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, 4-trifluoromethoxybenzyl, 4-methoxycarbonyl-benzyl, 2,3-dimethoxybenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,4-difluorobenzyl, 2,5-difluorobenzyl, 3,4,5-trimethoxybenzyl, 2,4,6-trimethoxybenzyl, 3-nitrobenzyl, 4-nitrobenzyl, 2,4-dimethoxybenzyl, 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 3,4-difluorobenzyl, 3,5-di(trifluoromethyl)-benzyl, 2-phenylethyl, 2-(4-

bromophenyl)ethyl, 2-(3-methoxyphenyl)ethyl, 2-(4-methoxyphenyl)ethyl, 2-(3,4-dimethoxyphenyl)ethyl, 2-(2-nitro-4,5-dimethoxy-phenyl)ethyl, 3-(4-morpholinyl)-n-propyl, 2-(4-morpholinyl)ethyl, 2-(4-imidazolyl)ethyl, 1-adamantanyl, 1-adamantanyl-methyl, 2-(2,5-dimethoxy-2,5-dihydro-furyl)methyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridyl-methyl, 3-pyridyl-methyl, 4-pyridyl-methyl, 2-(3,4-dimethyl-pyridyl), 2-(5-bromopyridyl), 2-(4,6-dimethyl-pyridyl), 2-(5-methyl-pyridyl), 3-(6-methoxy-pyridyl), thienylmethyl, 2-thienylethyl, 1-naphthyl, 1-naphthyl-methyl, 1-(3,4-methylenedioxyphenyl)methyl, 2-(3,4-methylenedioxyphenyl)ethyl, 2-furyl-



methyl, , 2S-hydroxy-S-cyclopentyl-methyl, 2S-hydroxy-S-cyclohexyl-methyl, 2S-hydroxy-S-cycloheptyl-methyl and 2-phenoxy-ethyl;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 1-(4-(3-trifluoromethyl-phenyl)-piperazinyl), 1-(4-phenyl-piperidinyl), 1-(4-piperidinyl-piperidinyl), 1-(4-(3,4-methylenedioxyphenyl-methyl)-piperazinyl), 1-(3-(diethylaminocarbonyl)-piperidinyl), 1-(4-[(4-chlorophenyl)-phenylmethyl]-piperiazinyl), 2-(1,2,3,4-tetrahydro-isoquinolinyl), 1-(4-t-butoxycarbonyl-piperazinyl), 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 4-(2,6-dimethyl-morpholinyl), 1-(4-benzyl-piperazinyl), 1-(3,5-dimethyl-piperidinyl), 1-(3-hydroxymethyl-piperidinyl), 1-(3-ethoxycarbonyl-piperidinyl), 1-(4-(ethoxycarbonyl)-piperidinyl), 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, 1-imidazolyl, 1-(2,3-dihydro-pyrrolidinyl), and 1-(2-(phenylamino-methyl)-N-pyrrolidinyl);

p is an integer from 0 to 1;

R^5 is selected from the group consisting of methyl, n-propyl and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

7. A compound as in Claim 4 wherein

R^0 is $-CH_2-CH(OH)-CH_2-X$;

X is $-NR^1R^2$;

R^1 is selected from the group consisting of hydrogen, 2-(3,4-dimethoxyphenyl)-ethyl, 1-(3,4-dimethoxyphenyl)-n-ethyl and amino-n-propyl;

R^2 is selected from the group consisting of hydrogen, methyl, n-butyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, t-butoxycarbonylamino-n-propyl, N-methyl-N-t-butoxycarbonyl-amino-n-ethyl, 3-nitrobenzyl, 4-methoxycarbonyl-benzyl, $-CH(CH_3)$-phenyl, 4-pyridinyl, 1-(4-ethoxycarbonyl-piperidinyl) and 2-(3H-imidazol-4-yl)-ethyl;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 1-pyrrolidinyl, 1-(3-hydroxy-pyrrolidinyl), 1-(3-(S)-hydroxy-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(4-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-methylamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(4-dimethylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl);

R^3 is selected from the group consisting of phenyl and 4-fluorophenyl;

L^1 is selected from the group consisting of $-CH_2-$ and $-CH_2CH_2-$;

 is selected from the group consisting cyclooctyl, 1-naphthyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, bicyclo[3.1.1.]hepten-2-yl, bicyclo[3.1.1]heptyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl.

p is an integer from 0 to 1;

R^5 is methyl;

q is 0;

or a pharmaceutically acceptable salt thereof.

8. A compound as in Claim 7 wherein

R^1 is selected from the group consisting of hydrogen, 1-(3,4-dimethoxyphenyl)-n-ethyl and amino-n-propyl;

R^2 is selected from the group consisting of hydrogen, methyl, n-butyl, 3-hydroxy-n-propyl, 3-methoxy-n-propyl, methylamino-n-propyl, dimethylamino-n-propyl, N-methyl-N-t-butoxycarbonyl-amino-n-ethyl, 3-nitrobenzyl, 4-methoxycarbonyl-benzyl, -CH(CH_3)-phenyl, 4-pyridinyl and 2-(3H-imidazol-4-yl)-ethyl;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a group selected from 2-(1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolinyl), 1-(4-[(4-chlorophenyl)-phenyl-methyl]-piperazinyl), 1-pyrrolidinyl, 1-(3-hydroxy-pyrrolidinyl), 1-(3-(R)-hydroxy-pyrrolidinyl), 1-(4-hydroxy-piperidinyl), 1-(3-(R)-dimethylamino-pyrrolidinyl), 1-(4-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-t-butoxycarbonylamino-pyrrolidinyl), 1-(3-(R)-amino-pyrrolidinyl), 1-(3-(S)-amino-pyrrolidinyl), 1-(3-(R)-methylamino-pyrrolidinyl), 1-(3-(S)-methyamino-pyrrolidinyl), 1-(3-(S)-ethylamino-pyrrolidinyl), 1-(4-dimethylamino-pyrrolidinyl), 1-(3-(N-methyl-N-t-butoxycarbonyl-amino-pyrrolidinyl) or 1-(2-(3,5-dichlorophenyl)-3-methyl-5-carboxy-1,2,4-triazolyl);



is selected from the group consisting cyclooctyl, 1-naphthyl, 1-acenaphthenyl, R-1-acenaphthenyl, S-1-acenaphthenyl, bicyclo[3.1.1.]hepten-2-yl, bicyclo[3.1.1]heptyl and (3aS)-2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl.

or a pharmaceutically acceptable salt thereof.

9. A compound as in Claim 1 selected from the group consisting of

8-(R) acenaphthen-1-yl-3-(3-amino-2-(S)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R) acenaphthen-1-yl-3-(3-amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R)-Acenaphthen-1-yl-3-(3-dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Dimethylamino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

8-(R)-Acenaphthen-1-yl-1-(4-fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxymethyl-piperidin-1-yl)-propyl]-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-8-cyclooctyl-1-(4-fluoro-phenyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-Amino-2-(R)-hydroxy-propyl)-1-(4-fluoro-phenyl)-8-1-(S)-(3aS)-(2,3,3a,4,5,6-hexahydro-1H-phenalen-1-yl)-1,3,8-triaza-spiro[4.5]decan-4-one;

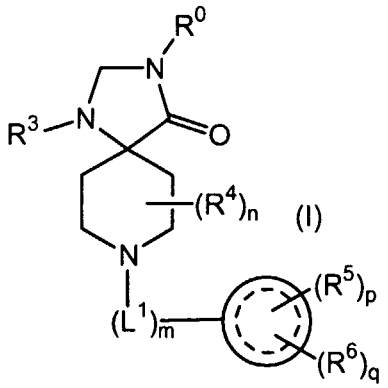
1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-hydroxy-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

1-(4-Fluoro-phenyl)-3-[2-(R)-hydroxy-3-(3-methylamino-propylamino)-propyl]-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one;

3-[3-(3-Dimethylamino-propylamino)-2-(R)-hydroxy-propyl]-1-(4-fluoro-phenyl)-8-(8-methyl-naphthalen-1-ylmethyl)-1,3,8-triaza-spiro[4.5]decan-4-one

and pharmaceutically acceptable salts thereof.

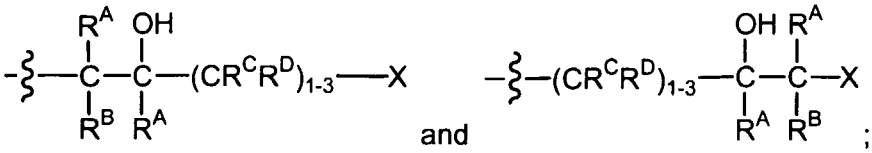
10. A compound of the formula (I)



(I)

wherein

R^0 is selected from the group consisting of



each R^A and R^B is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

each R^C and R^D is independently selected from the group consisting of hydrogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl; wherein the aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl substituent is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, nitro, cyano or $N(R^E)_2$;

each R^E is independently selected from the group consisting of hydrogen and C_{1-4}alkyl;

X is selected from the group consisting of $-NR^1R^2$, $-C(O)-NR^1R^2$, $-NR^1-C(O)-R^2$, $-OR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-S-(C_{2-4}alkyl)-NR^1R^2$, $-S-(C_{2-4}alkyl)-C(O)O-C(CH_3)_3$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ and $-SO_2-(C_{1-4}alkyl)-NR^1R^2$; wherein the alkyl portion of the $-S-(C_{2-4}alkyl)-NR^1R^2$, $-SO-(C_{1-4}alkyl)-NR^1R^2$ or $-SO_2-(C_{1-4}alkyl)-NR^1R^2$ group is optionally substituted with one or more substituents independently selected from carboxy, hydroxy, hydroxyC_{1-4}alkyl, C_{1-4}alkyl, C_{1-4}alkoxycarbonyl or $-CONR^1R^2$;

each R^1 and R^2 is independently selected from the group consisting of hydrogen, C_{1-8}alkyl, C_{1-8}alkoxy, cycloalkyl, cycloalkyl-C_{1-4}alkyl, partially unsaturated carbocylyl, aryl, arC_{1-4}alkyl, arC_{1-4}alkoxy, heteroaryl, heteroaryl-C_{1-4}alkyl, heterocycloalkyl, heterocycloalkyl-C_{1-4}alkyl, $-C(O)-C_{1-6}$alkyl, -C(O)-aryl, $-C(O)-arC_{1-4}$alkyl, -C(O)-heteroaryl and -C(O)-heterocycloalkyl; wherein the C_{1-8}alkyl, cycloalkyl, partially unsaturated carbocyclyl, aryl, arC_{1-8}alkyl, heteroaryl or heterocycloalkyl group, whether alone or part of a substituent group, is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $-C(O)-C_{1-4}$alkyl, C_{1-4}alkoxycarbonyl, $N(R^E)_2$, $N(R^E)_2-C_{1-4}$alkyl, $N(R^E)-C(O)C(CH_3)_3$, aryl, aryloxy, cycloalkyl, heteroaryl, aryl substituted heteroarylaminosulfonyl or C_{1-6}alkylthio;

alternatively when R^1 and R^2 are both bound to the same nitrogen atom, R^1 and R^2 are taken together with the nitrogen atom to which they are bound to form a heteroaryl or heterocycloalkyl group; wherein the heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxycarbonyl, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$, aryl, arC_{1-4}alkyl, heteroaryl, heterocycloalkyl, di(C_{1-6})alkylamino-carbonyl, t-butoxycarbonyl or arylamino-C_{1-4}alkyl; wherein the aryl, arC_{1-4}alkyl, heteroaryl or heterocycloalkyl substituent is optionally further substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, $N(R^E)_2$ or substituted phenyl; wherein the substituents on the phenyl are one or more independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

R^3 is selected from the group consisting of aryl, arC_{1-6}alkyl and heteroaryl; wherein the aryl, arC_{1-6}alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4}alkyl and hydroxy substituted C_{1-4}alkyl;

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6}alkyl and C_{3-6}alkenyl; wherein the double bond of the C_{3-6}alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6}alkyl or C_{3-6}alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6}alkyl, fluorinated C_{1-6}alkyl or C_{1-6}alkoxy;

 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, NR^1R^2, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO-NR^1R^2, -SO_2-NR^1R^2 and -C(O)-NR^1R^2;

q is an integer from 0 to 1;

R^6 is selected from the group consisting of -$(L^2)_{0-1}$-R^7;

L^2 is selected from the group consisting of -C_{1-6}alkyl-, -C_{2-4}alkenyl-, -C_{2-6}alkynyl-, -O-, -S-, -NH-, -N(C_{1-4}alkyl)-, -C_{1-6}alkyl-O-, -C_{1-6}alkyl-S-, -O-C_{1-6}alkyl-, -S-C_{1-6}alkyl-, -O-C_{2-6}alkyl-O-, -S-C_{2-6}alkyl-S-, -SO_2-, -SO_2NH-, -SO_2N(C_{1-4}alkyl)-, -NH-SO_2-, -N(C_{1-4}alkyl)-SO_2-, -C(O)-O- and -O-C(O)-;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO_2-$N(R^E)_2$ and -C(O)-$N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of Claim 1.

12. A pharmaceutical composition made by mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

13. A process for making a pharmaceutical composition comprising mixing a compound of Claim 1 and a pharmaceutically acceptable carrier.

14. A method of treating a disorder mediated by the ORL-1 receptor, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Claim 1.

15. The method of Claim 14, wherein the disorder mediated by the ORL-1 receptor is selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, improved cognition, improved memory and mood stabilization.

16. A method of treating a disorder mediated by the ORL-1 receptor, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 11.

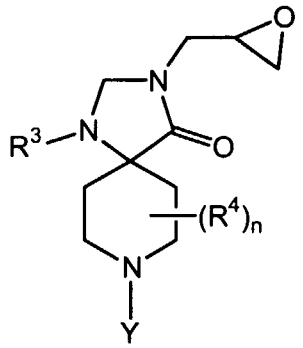
17. A method of treating a condition selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, improved cognition, improved memory and mood stabilization, in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of Claim 1.

18. A method of treating a condition selected from the group consisting of anxiety, depression, panic, mania, dementia, bipolar disorder, substance abuse, neuropathic pain, acute pain, chronic pain, migraine, asthma, cough, psychosis, schizophrenia, epilepsy, hypertension, obesity, eating disorders, cravings, diabetes, cardiac arrhythmia, irritable bowel syndrome, Crohn's disease, urinary incontinence, adrenal disorders, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, improved cognition, improved memory and mood stabilization, in a subject in

need thereof comprising administering to the subject a therapeutically effective amount of the composition of Claim 7.

19. The use of a compound as in Claim 1 for the preparation of a medicament for the treatment of (a) anxiety, (b) depression, (c) panic, (d) mania, (e) dementia, (f) bipolar disorder, (g) substance abuse, (h) neuropathic pain, (i) acute pain, (j) chronic pain, (k) migraine, (l) asthma, (m) cough, (n) psychosis, (o) schizophrenia, (p) epilepsy, (q) hypertension, (r) obesity, (s) eating disorders, (t) cravings, (u) diabetes, (v) cardiac arrhythmia, (w) irritable bowel syndrome, (x) Crohn's disease, (y) urinary incontinence, (z) adrenal disorders, (aa) attention deficit disorder (ADD), (bb) attention deficit hyperactivity disorder (ADHD), (cc) Alzheimer's disease, for (dd) improved cognition, (ee) improved memory or (ff) mood stabilization, in a subject in need thereof.

20. A compound of the formula (E)



(E)

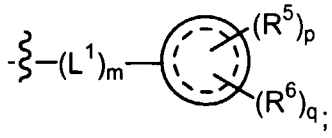
wherein

R^3 is selected from the group consisting of aryl, arC_{1-6}alkyl and heteroaryl; wherein the aryl, arC_{1-6}alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

each R^E is independently selected from hydrogen or C_{1-4}alkyl;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4}alkyl and hydroxy substituted C_{1-4}alkyl;

Y is selected from the group consisting of hydrogen, C_{1-4}alkyl, t-butoxycarbonyl and ;

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6}alkyl and C_{3-6}alkenyl; wherein the double bond of the C_{3-6}alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6}alkyl or C_{3-6}alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6}alkyl, fluorinated C_{1-6}alkyl or C_{1-6}alkoxy;

 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6}alkyl, hydroxy substituted C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, NR^1R^2, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO-NR^1R^2, -SO_2-NR^1R^2 and -C(O)-NR^1R^2;

q is an integer from 0 to 1;

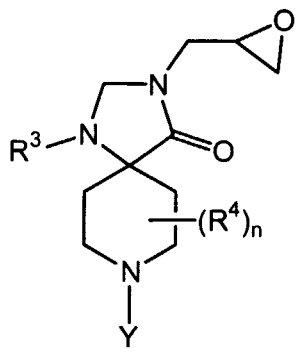
R^6 is selected from the group consisting of -$(L^2)_{0-1}$-R^7;

L^2 is selected from the group consisting of -C_{1-6}alkyl-, -C_{2-4}alkenyl-, -C_{2-6}alkynyl-, -O-, -S-, -NH-, -N(C_{1-4}alkyl)-, -C_{1-6}alkyl-O-, -C_{1-6}alkyl-S-, -O-C_{1-6}alkyl-, -S-C_{1-6}alkyl-, -O-C_{2-6}alkyl-O-, -S-C_{2-6}alkyl-S-, -SO_2-, -SO_2NH-, -SO_2N(C_{1-4}alkyl)-, -NH-SO_2-, -N(C_{1-4}alkyl)-SO_2-, -C(O)-O- and -O-C(O)-;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, -SO_2-$N(R^E)_2$ and -C(O)-$N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.

21. A compound of the formula (E)



(E)

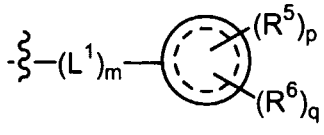
wherein

R^3 is selected from the group consisting of aryl, arC_{1-6}alkyl and heteroaryl; wherein the aryl, arC_{1-6}alkyl or heteroaryl group is optionally substituted with one or more substituents independently selected from halogen, hydroxy, carboxy, C_{1-4}alkyl, C_{1-4}alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano or $N(R^E)_2$;

each R^E is independently selected from hydrogen or C_{1-4}alkyl;

n is an integer from 0 to 2;

R^4 is selected from the group consisting of hydroxy, C_{1-4}alkyl and hydroxy substituted C_{1-4}alkyl;

Y is selected from the group consisting of hydrogen, C_{1-4}alkyl, t-butoxycarbonyl and ;

m is an integer from 0 to 1;

L^1 is selected from the group consisting of C_{1-6}alkyl and C_{3-6}alkenyl; wherein the double bond of the C_{3-6}alkenyl group is at least one carbon atom removed from the attachment point to the N atom; and wherein the C_{1-6}alkyl or C_{3-6}alkenyl group is optionally substituted with one to two substituents independently selected from hydroxy, fluoro, C_{1-6}alkyl, fluorinated C_{1-6}alkyl or C_{1-6}alkoxy;

 is selected from the group consisting of cycloalkyl, partially unsaturated carbocyclyl, aryl, heteroaryl and heterocycloalkyl;

p is an integer from 0 to 5;

R^5 is selected from the group consisting of hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, NR^1R^2, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, $-SO-NR^1R^2$, $-SO_2-NR^1R^2$ and $-C(O)-NR^1R^2$;

q is an integer from 0 to 1;

R^6 is selected from the group consisting of $-(L^2)_{0-1}-R^7$;

L^2 is selected from the group consisting of $-C_{1-6}$alkyl-, $-C_{2-4}$alkenyl-, $-C_{2-6}$alkynyl-, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)-$, $-C_{1-6}$alkyl-O-, $-C_{1-6}$alkyl-S-, $-O-C_{1-6}$alkyl-, $-S-C_{1-6}$alkyl-, $-O-C_{2-6}$alkyl-O-, $-S-C_{2-6}$alkyl-S-, $-SO_2-$, $-SO_2NH-$, $-SO_2N(C_{1-4}alkyl)-$, $-NH-SO_2-$, $-N(C_{1-4}alkyl)-SO_2-$, -C(O)-O- and -O-C(O)-;

R^7 is selected from the group consisting of aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl and heterocycloalkyl; wherein the aryl, partially unsaturated carbocyclyl, cycloalkyl, heteroaryl or heterocycloalkyl group is optionally substituted with one or more substituents independently selected from hydroxy, carboxy, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, nitro, cyano, $N(R^E)_2$, trifluoromethyl, trifluoromethoxy, C_{1-4}alkoxycarbonyl, $-SO_2-N(R^E)_2$ and $-C(O)-N(R^E)_2$;

or a pharmaceutically acceptable salt thereof.