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(54) Title: SUBSTITUTED ARYL SULFONE DERIVATIVES AS CALCIUM CHANNEL BLOCKERS

(57) Abstract: A series of substituted aryl sulfone derivatives represented by Formula I, or pharmaceutically acceptable salts thereof. Pharmaceutical compositions comprise an effective amount of the instant compounds, either alone, or in combination with one or more other therapeutically active compounds, and a pharmaceutically acceptable carrier. Methods of treating conditions associated with, or caused by, calcium channel activity, including, for example, acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain, urinary incontinence, itchiness, allergic dermatitis, epilepsy, diabetic neuropathy, irritable bowel syndrome, depression, anxiety, multiple sclerosis, sleep disorder, bipolar disorder and stroke, comprise administering an effective amount of the present compounds, either alone, or in combination with one or more other therapeutically active compounds.

TITLE OF THE INVENTION
SUBSTITUTED ARYL SULFONE DERIVATIVES AS CALCIUM CHANNEL BLOCKERS

FIELD OF THE INVENTION

This invention relates to a series of substituted aryl sulfone derivatives. In particular, this invention relates to substituted aryl sulfone derivatives that are N-type voltage-gated calcium channel blockers useful for the treatment of a variety of pain conditions including chronic and neuropathic pain. The compounds of the present invention also display activity in connection with blockage of T-type voltage-gated calcium channels. The compounds described in this invention are useful for the treatment of chronic and acute pain, including neuropathic, inflammatory, and visceral pain. The compounds described in this invention are also useful for the treatment of conditions including disorders of bladder function, pruritis, itchiness, allergic dermatitis and disorders of the central nervous system (CNS) such as stroke, epilepsy, essential tremor, schizophrenia, Parkinson's disease, manic depression, bipolar disorder, depression, anxiety, sleep disorder, diabetic neuropathy, hypertension, cancer, diabetes, infertility and sexual dysfunction.

BACKGROUND TO THE INVENTION

Ion channels control a wide range of cellular activities in both excitable and non-excitable cells (Hille, Bertil – "Ion Channels of Excitable Membranes", 3rd Edition, (2001), 814pp; Sinauer Associates, Sunderlan, Massachusetts, USA). Ion channels are attractive therapeutic targets due to their involvement in many physiological processes. In excitable cells, the coordinated function of the resident set of ion channels controls the electrical behavior of the cell. Plasma membrane calcium channels are members of a diverse superfamily of voltage gated channel proteins. Calcium channels are membrane-spanning, multi-subunit proteins that allow controlled entry of Ca2+ ions into cells from the extracellular fluid. Excitable cells throughout the animal kingdom, and at least some bacterial, fungal and plant cells, possess one or more types of calcium channel. Nearly all "excitable" cells in animals, such as neurons of the central nervous system (CNS), peripheral nerve cells and muscle cells, including those of skeletal muscles, cardiac muscles, and venous and arterial smooth muscles, have voltage-gated calcium channels. Voltage-gated calcium channels provide an important link between electrical activity at the plasma membrane and cell activities that are dependent on intracellular calcium, including muscle contraction, neurotransmitter release, hormone secretion and gene expression. Voltage-

gated calcium channels serve to integrate and transduce plasma membrane electrical activity into changes in intracellular calcium concentration, and can do this on a rapid time scale.

Multiple types of calcium channels have been identified in mammalian cells from various tissues, including skeletal muscle, cardiac muscle, lung, smooth muscle and brain. A major family of this type is the L-type calcium channels, which include $Ca_v1.1$, $Ca_v1.2$, $Ca_v1.3$, and $Ca_v1.4$, whose function is inhibited by the familiar classes of calcium channel blockers (dihydropyridines such as nifedipine, phenylalkylamines such as verapamil, and benzothiazepines such as diltiazem). Additional classes of plasma membrane calcium channels are referred to as T ($Ca_v3.1$, $Ca_v3.2$, and Cav3.3), N ($Ca_v2.2$), P/Q ($Ca_v2.1$) and R ($Ca_v2.3$). The "T-type" (or "low voltage-activated") calcium channels are so named because they open for a shorter duration (T=transient) than the longer (L=long-lasting) openings of the L-type calcium channels. The L, N, P and Q-type channels activate at more positive potentials (high voltage activated) and display diverse kinetics and voltage-dependent properties.

Because of the crucial role in cell physiology, modulation of calcium channel activity can have profound effects. Mutations in calcium channel subunits have been implicated in a number of genetic diseases including familial hemiplegic migraine, spinocerebellar ataxia, Timothy Syndrome, incomplete congenital stationary night blindness and familial hypokalemic periodic paralysis. Modulation of voltage-gated calcium channels by signaling pathways, including c-AMP-dependent protein kinases and G proteins is an important component of signaling by hormones and neurotransmitters (Catteall, W. A., *Ann. Rev. Cell and Dev. Biol.*, 16, 521-555, (2000)). Pharmacological modulation of calcium channels can have significant therapeutic effects, including the use of L-type calcium channel ($Ca_v1.2$) blockers in the treatment of hypertension (Hockerman, G. H et. al, *Proc. Natl Acad Sci. (USA)*, 94, 14906-1491, (1997)) and more recently, use of Ziconitide, a peptide blocker of N-type calcium channels ($Ca_v2.2$), for the treatment of intractable pain (Staals, P. S. et. al, *JAMA*, 291, 63-70, (2004)). Zicontide is derived from Conotoxin, a peptide toxin isolated from cone snail venom, must be applied by intrathecal injection to allow its access to a site of action in the spinal cord and to minimize exposure to channels in the autonomic nervous system that are involved in regulating cardiovascular function. Ziconotide has also been shown to highly effective as a neuroprotective agent in rat models of global and focal ischemia (Colburne et. Al., *Stroke* ,30, 662-668 (1999)) suggesting that modulation of N-type calcium channels ($Ca_v2.2$) has implication in the treatment of stroke.

Clinical and preclinical experiments with ziconitide and related peptides confirm a key role of N-type calcium channels in transmitting nociceptive signals into the spinal cord. Identification of N-type calcium channel blockers that can be administered systemically, and effectively block N-type calcium channels in the nociceptive signaling pathway, while sparing N-

type calcium channel function in the periphery would provide important new tools for treating some forms of pain. The present invention describes blockers of N-type calcium channels ($Ca_v2.2$) that display functional selectivity by blocking N-type calcium channel activity needed to maintain pathological nociceptive signaling, while exhibiting a lesser potency at blocking N-type calcium channels involved in maintaining normal cardiovascular function.

There are three subtypes of T-type calcium channels that have been identified from various warm blooded animals including rat [*J Biol. Chem.*276(6) 3999-4011 (2001); *Eur J Neurosci* 11(12):4171-8 (1999); reviewed in *Cell Mol Life Sci* 56(7-8):660-9 (1999)]. These subtypes are termed α1G, α1H, and α1I, and the molecular properties of these channels demonstrate 60-70% homology in the amino acid sequences. The electrophysiological characterization of these individual subtypes has revealed differences in their voltage-dependent activation, inactivation, deactivation and steady-state inactivation levels and their selectivity to various ions such as barium (*J Biol. Chem.*276(6) 3999-4011 (2001)). Pharmacologically, these subtypes have shown differing sensitivities to blockade by ionic nickel. These channel subtypes are also expressed in various forms due to their ability to undergo various splicing events during their assembly (*J Biol. Chem.*276 (6) 3999-4011 (2001)).

US Pat. Nos. 6,011,035; 6,294,533; and 6,617,322; and publication numbers WO2007/075525, US2004/044004, JP2002/088073, WO2007085357, W2007028638, WO94/22835, US20030408, and WO2004/096217, describe calcium channel blockers in the treatment of pain. . See also WO2004/031138, WO2003084948, WO2003/075853, WO2001/025200, WO2007056075, WO2005000798 and WO2002/055516.

T-type calcium channels have been implicated in pathologies related to various diseases and disorders, including epilepsy, essential tremor, pain, neuropathic pain, schizophrenia, Parkinson's disease, depression, anxiety, sleep disorders, sleep disturbances, psychosis, schizophrenia, cardiac arrhythmia, hypertension, pain, cancer, diabetes, infertility and sexual dysfunction (*J Neuroscience*, 14, 5485 (1994); *Drugs Future* 30(6), 573-580 (2005); *EMBO J*, 24, 315-324 (2005); *Drug Discovery Today*, 11, 5/6, 245-253 (2006)).

SUMMARY OF THE INVENTION

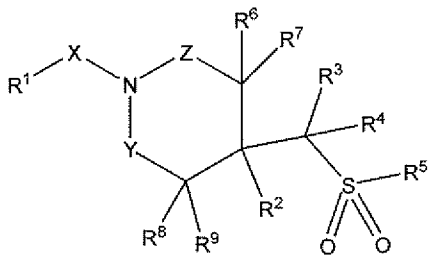
The present invention is directed to a series of substituted aryl sulfone derivatives that are N-type calcium channel (Cav2.2) blockers useful for the treatment of acute pain, chronic pain, cancer pain, visceral pain, inflammatory pain, neuropathic pain, post-herpetic neuralgia, diabatic neuropathy, trigeminal neuralgia, migrane, fibromyalgia and stroke. The compounds of

the present invention also display activities on T-type voltage-activated calcium channels (Cav 3.1 and Cav 3.2). The compounds described in this invention are also useful for the treatment of other conditions, including disorders of bladder function, pruritis, itchiness, allergic dermatitis and disorders of the central nervous system (CNS) such as stroke, epilepsy, essential tremor, schizophrenia, Parkinson's disease, manic depression, bipolar disorder, depression, anxiety, sleep disorder, hypertension, cancer, diabetes, infertility and sexual dysfunction. This invention also provides pharmaceutical compositions comprising a compound of the present invention, either alone, or in combination with one or more therapeutically active compounds, and a pharmaceutically acceptable carrier. The compounds of the present invention provide greater stability and maintain Cav2.2 potency and efficacy than prior known sulfonamides.

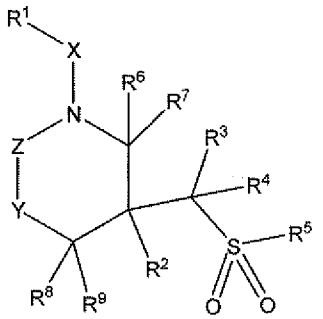
This invention further comprises methods for the treatment of acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain and disorders of the CNS including, but not limited to, epilepsy, manic depression, depression, anxiety and bipolar disorder comprising administering the compounds and pharmaceutical compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are represented by Formula I and Formula II:



(I)



(II)

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof:

X is a bond, $CR^{10}R^{11}$, C=O, $C=ONR^{10}$, CO_2, SO_2, C_{6-10} aryl, or C_{5-10} heteroaryl;
Y is $CR^{10}R^{11}$, C=O or absent;
Z is $CR^{10}R^{11}$, C=O or absent;
R^1 is H, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, OR^{10}, $C(O)R^{10}$, $(CH_2)_nC_{5-10}$ heterocycle, $(CH_2)_nC_{6-10}$ aryl, $(CH_2)_nC_{5-10}$ heteroaryl, fused aryl or fused heteroaryl, wherein said alkyl, cycloalkyl, heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a;
R^2 is H, C_{1-4} alkyl and C_{1-4}-perfluoroalkyl, C_{3-5}-cycloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, F, Cl, CN, $NR^{10}R^{11}$, wherein said alkyl, cycloalkyl, aryl and heteroaryl is optionally substituted with one to three groups of R^a;
R^3 and R^4 are each and independently selected from H, or C_{1-6} alkyl, C_{1-4}-perfluoroalkyl, C_{3-7}-cycloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, F, Cl, CN, OR^{10}, $NR^{10}R^{11}$, SO_2R^{10}, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONHR^{10}$, $CONR^{10}R^{11}$, or R^3 and R^4 join to form a 3-7 member carbocyclic or heterocyclic ring, wherein said alkyl, cycloalkyl, heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a;
R^5 is C_{6-10} aryl, C_{5-10} heteroaryl, C_{3-7} cycloalkyl, C_{5-10} heterocycle, wherein said cycloalkyl, heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a;
R^6, R^7, R^8, and R^9 independently represent H, C_{1-4}alkyl and C_{1-4}perfluoroalkyl, C_{3-6}-cycloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, F, Cl, CN, OR^{10}, $NR^{10}R^{11}$, or R^8 and R^9 combined with the carbon atom they are attached to can form C(O);
R^{10} and R^{11} are each and independently selected from H, or C_{1-6}alkyl, $(CH_2)_nC_{1-4}$-fluoroalkyl, C_{3-7}cycloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, or R^{10} and R^{11} join to form a 3-7 member

carbocyclic or heterocyclic ring with the atom to which they are attached; said alkyl, aryl, or heteroaryl optionally substituted with 1 to 3 groups of R^a,
n represents 0 to 6, and
R^a represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4}-fluoroalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, halogen, CN, $-OCF_3$, $-OCHF_2$, $-C(O)CF_3$, $-C(OR^{10})(CF_3)_2$, SR^{10}, $-OR^{10}$, $NR^{10}R^{11}$, SOR^{10}, SO_2R^{10}, $NR^{10}COR^{11}$, $NR^{10}COOR^{11}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, said aryl and heteroaryl optionally substituted with 1 to 3 groups of C_{1-6} alkyl, C_{3-7} cycloalkyl, halogen, CF_3, CN or OR^{10}; with the provisio that at least one of Y or Z is C=O.

One embodiment of the present invention is realized when X is C=O and R^1 is $(CH_2)_nC_{5-10}$ heterocycle, $(CH_2)_nC_{6-10}$ aryl, $(CH_2)_nC_{5-10}$ heteroaryl, fused aryl or fused heteroaryl, wherein said heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a and all other variables are as described herein. A sub-embodiment of this invention is realized when R^1 is phenyl, or pyridyl optionally substituted with 1 to 3 groups of R^a, and all other variables are as described herein. Still another sub-embodiment of this invention is realized when R^a is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4}-fluoroalkyl halogen, CN, $-OCF_3$, $-OCHF_2$, OR^{10}, or SO_2R^{10}.

Another embodiment of the present invention is realized when X is C=O and R^1 is C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to three groups of R^a and all other variables are as described herein.

Another embodiment of the present invention is realized when X is C=O and R^5 is C_{6-10} aryl, C_{5-10} heteroaryl, or C_{5-10} heterocycle, wherein said heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a and all other variables are as described herein. A sub-embodiment of this invention is realized when R^5 is phenyl, or pyridyl, optionally substituted with 1 to 3 groups of R^a, and all other variables are as described herein. Still another sub-embodiment of this invention is realized when R^a is C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4}-fluoroalkyl halogen, CN, $-OCF_3$, $-OCHF_2$, OR^{10}, or SO_2R^{10}.

In another embodiment of the present invention X is C_{6-10} aryl, or C_{5-10} heteroaryl and all other variables are as described herein.

In another embodiment of the present invention X is C=O and all other variables are as described herein.

In another embodiment of the present invention Y is absent and all other variables are as described herein.

In another embodiment of the present invention Y is $CR^{10}R^{11}$, and all other variables are as described herein.

In another embodiment of the present invention Y is C=O and all other variables are as described herein.

In another embodiment of the present invention Z is C=O and all other variables are as described herein.

In still another embodiment of the present invention Z is absent and all other variables are as described herein.

In another embodiment of the present invention Z is $CR^{10}R^{11}$ and all other variables are as described herein.

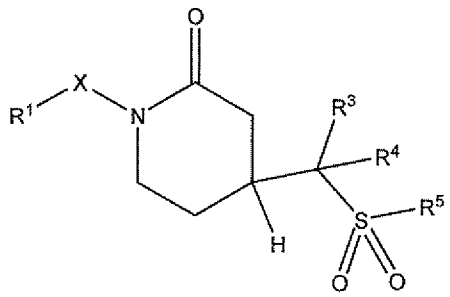
In another embodiment of the present invention R^1 is phenyl optionally substituted with 1 to 3 groups of R^a and all other variables are as described herein.

In another embodiment of the present invention R^1 is pyridyl optionally substituted with 1 to 3 groups of R^a and all other variables are as described herein.

In another embodiment of the present invention R5 is phenyl optionally substituted with 1 to 3 groups of R^a and all other variables are as described herein.

In another embodiment of the present invention R^5 is pyridyl optionally substituted with 1 to 3 groups of R^a and all other variables are as described herein.

In yet another embodiment of the present invention, Y and Z are CH_2 and CO, respectively, and R^6, R^7, R^8, and R^9 are each H and all other variables are as described herein, as depicted in formula Ia:

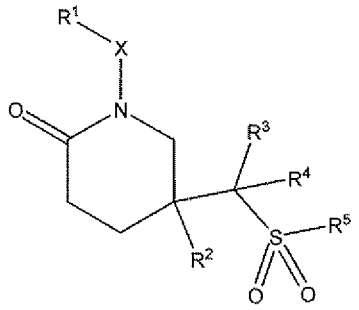


Ia

A sub-embodiment of structural formula Ia is realized when X is C=O. A further sub-embodiment is realized when both R^3 and R^4 are H or CH_3, or one of R^3 and R^4 is H and the other is CH_3, with the resulting stereocenter having either the *R* or *S* stereochemical configuration. Still another sub-embodiment of this invention is realized when R^1 is C_{1-6} alkyl, phenyl, or pyridyl all optionally substituted with 1 to 3 groups of R^a. Yet another sub-embodiment of this invention is realized when R^5 is phenyl or pyridyl optionally substituted with 1 to 3 groups of R^a. Another sub-embodiment of this invention is realized when both R^1 and R^5 are phenyl, optionally substituted with 1 to 3 groups of R^a. Another sub-embodiment of this

invention is realized one of R^1 and R^5 is phenyl and the other is pyridyl, said phenyl and pyridyl optionally substituted with 1 to 3 groups of R^a.

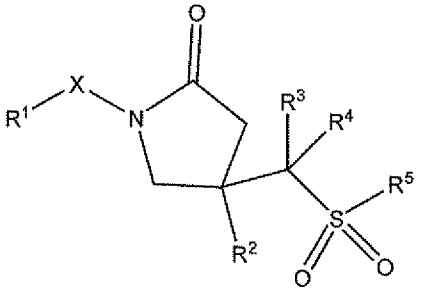
In another embodiment of the present invention, Y and Z are CH_2 and CO, respectively, and R^6, R^7, R^8, and R^9 are each H and all other variables are as described herein, as depicted in formula Ia:



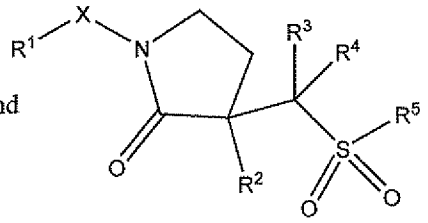
IIa

A sub-embodiment of structural formula IIa is realized when X is C=O. A further sub-embodiment is realized when both R^3 and R^4 are H or CH_3, or one of R^3 and R^4 is H and the other is CH_3, with the resulting stereocenter having either the *R* or *S* stereochemical configuration. Still another sub-embodiment of this invention is realized when R^1 is C_{1-6} alkyl, phenyl, or pyridyl all optionally substituted with 1 to 3 groups of R^a. Yet another sub-embodiment of this invention is realized when R^5 is phenyl or pyridyl optionally substituted with 1 to 3 groups of R^a. Another sub-embodiment of this invention is realized when both R^1 and R^5 are phenyl, optionally substituted with 1 to 3 groups of R^a. Another sub-embodiment of this invention is realized one of R^1 and R^5 is phenyl and the other is pyridyl, said phenyl and pyridyl optionally substituted with 1 to 3 groups of R^a.

In still another embodiment of the present invention one of Y and Z is C=O and the other is absent, and R^6, R^7, R^8, and R^9 are each H and all other variables are as described herein, as depicted in formula IIIa and IIIb:



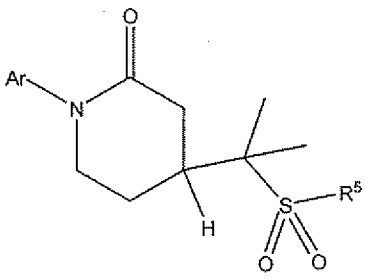
and



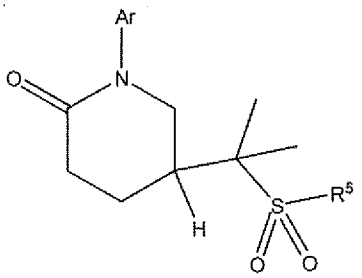
IIIa IIIb.

A sub-embodiment of structural IIa and IIb is realized when X is C=O and R^2 is H. A further sub-embodiment of this invention is realized when both R^3 and R^4 are CH_3. Still another sub-embodiment of this invention is realized when R1 is C_{1-6} alkyl, phenyl, or pyridyl all optionally substituted with 1 to 3 groups of R^a. Yet another sub-embodiment of this invention is realized when R^5 is phenyl or pyridyl optionally substituted with 1 to 3 groups of R^a. Another sub-embodiment of this invention is realized when both R1 and R^5 are phenyl, optionally substituted with 1 to 3 groups of R^a. Another sub-embodiment of this invention is realized one of R1 and R^5 is phenyl and the other is pyridyl, said phenyl and pyridyl optionally substituted with 1 to 3 groups of R^a.

In another embodiment of the compounds of the present invention, Ar is aryl, one of Y and Z is C=O and the other is CH_2, R^2 is H, and both R^3 and R^4 are CH_3, and R^6, R^7, R^8, and R^9 are each H and all other variables are as described herein, as depicted in IVa and IVb:



and

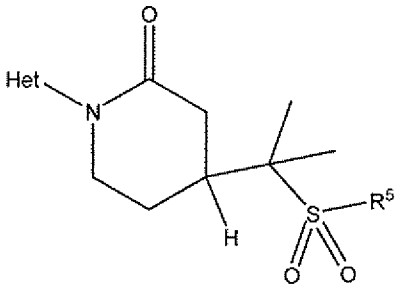


IVa IVb

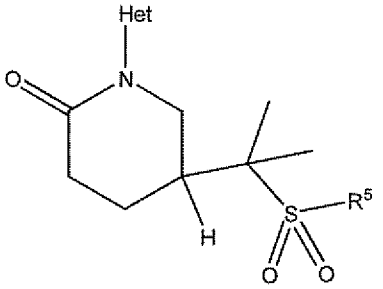
A sub-embodiment of this invention is realized when Ar is phenyl, optionally substituted with 1 to 3 groups of R^a. Yet another sub-embodiment of this invention is realized when R^5 is phenyl or pyridyl optionally substituted with 1 to 3 groups of R^a. Another sub-embodiment of this invention is realized when both Ar and R^5 are phenyl, optionally substituted with 1 to 3 groups

of R^a. Another sub-embodiment of this invention is realized when R^5 is pyridyl, said phenyl and pyridyl optionally substituted with 1 to 3 groups of R^a.

In another embodiment of the present invention, Het is heteroaryl, one of Y and Z is C=O and the other CH_2, R^2 is H, both R^3 and R^4 are CH_3, and R^6, R^7, R^8, and R^9 are each H and all other variables are as described herein, as depicted in Va and Vb:



and



Va Vb

A sub-embodiment of formula Va and Vb invention is realized when Het is pyridyl optionally substituted with 1 to 3 groups of R^a. Yet another sub-embodiment of this invention is realized when R^5 is phenyl or pyridyl optionally substituted with 1 to 3 groups of R^a. Another sub-embodiment of this invention is realized when R^5 is phenyl, optionally substituted with 1 to 3 groups of R^a.

When any variable (e.g. aryl, heterocycle, R^1, R^5 etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

When R^a is –O- and attached to a carbon it is referred to as a carbonyl group and when it is attached to a nitrogen (e.g., nitrogen atom on a pyridyl group) or sulfur atom it is referred to a N-oxide and sulfoxide group, respectively.

As used herein, "alkyl" encompasses groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, and alkynyl and means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, and heptyl. "Alkenyl" refers to a hydrocarbon radical straight, branched or cyclic containing from 2 to 10 carbon atoms and at least one carbon to carbon double bond. Preferred alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl. Preferably, alkenyl is C_2-C_6 alkenyl. Preferred alkynyla are C_2-C_6 alkynyl. "Alkenyl," "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

As used herin, "fluoroalkyl" refers to an alkyl substituent as described herin containing at least one flurine substituent.

The term "cycloalkyl" refers to a saturated hydrocarbon containing one ring having a specified number of carbon atoms. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

The term "C_{1-6}" includes alkyls containing 6, 5, 4, 3, 2, or 1 carbon atoms

The term "alkoxy" as used herein, alone or in combination, includes an alkyl group connected to the oxy connecting atom. The term "alkoxy" also includes alkyl ether groups, where the term 'alkyl' is defined above, and 'ether' means two alkyl groups with an oxygen atom between them. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, methoxymethane (also referred to as 'dimethyl ether'), and methoxyethane (also referred to as 'ethyl methyl ether').

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, napthyl, tetrahydronapthyl, indanyl, or biphenyl.

The term heterocycle, heterocyclyl, or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. The term heterocycle or heterocyclic includes heteroaryl moieties. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, 1,3-dioxolanyl, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide,

thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl. An embodiment of the examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, 2-pyridinonyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, thienyl and triazolyl.

In certain embodiments, the heterocyclic group is a heteroaryl group. As used herein, the term "heteroaryl" refers to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, between one and about three heteroatoms selected from the group consisting of N, 0, and S. heteroaryl groups include, without limitation, thienyl, benzothienyl, furyl, benzofuryl, dibenzofuryl, pyrrolyl, imidazolyl, pyrazoiyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, quinolyl, isoquinolyl, quinoxalinyl, tetrazolyl, oxazolyl, thiazolyl, and isoxazolyl.

In certain other embodiments, the heterocyclic group is fused to an aryl or heteroaryl group. Examples of such fused heterocycles include, without limitation, tetrahydroquinolinyl and dihydrobenzofuranyl.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heterocyclic ring system which contains an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole, benzisothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole,

naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene, triazine, triazole, and N-oxides thereof.

Examples of heterocycloalkyls include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "heteroatom" means O, S or N, selected on an independent basis.

A moiety that is substituted is one in which one or more hydrogen atoms have been independently replaced with another chemical substituent. As a non-limiting example, substituted phenyls include 2-flurophenyl, 3,4-dichlorophenyl, 3-chloro-4-fluoro-phenyl, 2,4fluor-3-propylphenyl. As another non-limiting example, substituted n-octyls include 2,4 dimethyl-5-ethyl-octyl and 3-cyclopentyloctyl. Included within this definition are methylenes (-CH_2-) substituted with oxygen to form carbonyl (-CO-).

Unless otherwise stated, as employed herein, when a moiety (e.g., cycloalkyl, hydrocarbyl, aryl, alkyl, heteroaryl, heterocyclic, urea, etc.) is described as "optionally substituted" it is meant that the group optionally has from one to four, preferably from one to three, more preferably one or two, non-hydrogen substituents. Suitable substituents include, without limitation, halo, hydroxy, oxo (e.g., an annular -CH- substituted with oxo is -C(O)-), nitro, halohydrocarbyl, hydrocarbyl, aryl, aralkyl, alkoxy, aryloxy, amino, acylamino, alkylcarbamoyl, arylcarbamoyl, aminoalkyl, acyl, carboxy, hydroxyalkyl, , alkanesulfonyl, arenesulfonyl, alkanesulfonamido, arenesulfonamido, aralkylsulfonamido, alkylcarbonyl, acyloxy, cyano, and ureido groups. Preferred substituents, which are themselves not further substituted (unless expressly stated otherwise) are:

(a) halo, cyano, oxo, carboxy, formyl, nitro, amino, amidino, guanidino, and

(b) C_1-C_6 alkyl or alkenyl or arylalkyl imino, carbamoyl, azido, carboxamido, mercapto, hydroxy, hydroxyalkyl, alkylaryl, arylalkyl, C_1-C_8 alkyl, SO_2CF_3, CF_3, SO_2Me, C_1-C_8 alkenyl, C_1-C_8 alkoxy, C_1-C_8 alkoxycarbonyl, aryloxycarbonyl, C_2-C_8 acyl, C_2-C_8 acylamino, C_1-C_8 alkylthio, arylalkylthio, arylthio, C_1-C_8alkylsulfinyl, arylalkylsulfnyl, arylsulfnyl, C_1-C_8 alkylsulfonyl, arylalkylsulfonyl, arylsulfonyl, C_0-C_6 N-alkylcarbamoyl, C_2-C_{15} *N,N* dialkylcarbamoyl, C_3-C_7 cycloalkyl, aroyl, aryloxy, arylalkyl ether, aryl, aryl fused to a cycloalkyl or heterocycle or another aryl ring, C_3-C_7 heterocycle, or any of these rings fused or spiro-fused to a cycloalkyl, heterocyclyl, or aryl, wherein each of the foregoing is further optionally substituted with one more moieties listed in (a), above.

"Halogen" refers to fluorine, chlorine, bromine and iodine.

The term "mammal" "mammalian" or "mammals" includes humans, as well as animals, such as dogs, cats, horses, pigs and cattle.

Compounds described herein may contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers unless specifically stated otherwise.

The compounds of the present invention may contain one or more asymmetric centers and may thus occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures, and individual diastereomers.

It will be understood that, as used herein, references to the compounds of structural formula I and II are meant to also include the pharmaceutically acceptable salts, and also salts that are not pharmaceutically acceptable when they are used as precursors to the free compounds or in other synthetic manipulations.

The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N, N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and tromethamine.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric,

isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like.

The pharmaceutical compositions of the present invention comprise compounds of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. Such additional therapeutic agents can include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists, iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, xiv) neurontin (gabapentin), xv) pregabalin, and xvi) sodium channel blockers. The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The present compounds and compositions are useful for the treatment of chronic, visceral, inflammatory and neuropathic pain syndromes. They are useful for the treatment of pain resulting from traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, small fiber neuropathy, and diabetic neuropathy. The present compounds and compositions are also useful for the treatment of chronic lower back pain, phantom limb pain, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgias, and pain associated with cancer, chemotherapy, HIV and HIV treatment-induced neuropathy. Compounds of this invention may also be utilized as local anesthetics. Compounds of this invention are useful for the treatment of irritable bowel syndrome and related disorders, as well as Crohn's disease.

The instant compounds have clinical uses for the treatment of epilepsy and partial and generalized tonic seizures. They are also useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and for treating multiple sclerosis. The present compounds are useful for the treatment of tachy-arrhythmias. Additionally, the instant

compounds are useful for the treatment of neuropsychiatric disorders, including mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but not limited to, cows, sheep, goats, horses, dogs, cats guinea pigs, or other bovine, ovine, equine, canine, feline, rodent such as mouse, species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents, such as norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), α-adrenoreceptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, neurokinin-1 receptor antagonists, corticotropin releasing factor (CRF) antagonists, and pharmaceutically acceptable salts thereof.

Further, it is understood that compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions and disorders, as well as to prevent other conditions and disorders associated with calcium channel activity.

Creams, ointments, jellies, solutions, or suspensions containing the instant compounds can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01 mg/kg to about 140 mg/kg of body weight per day are useful in the treatment of inflammatory and neuropathic pain, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammatory pain may be effectively treated by the administration of from about 0.01mg to about 75 mg of the compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day. Neuropathic pain may be effectively treated by the administration of from about 0.01 mg to about 125 mg of the

compound per kilogram of body weight per day, or alternatively about 0.5 mg to about 5.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5 mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may ary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1 mg to about 1000 mg of the active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg or 1000 mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such patient-related factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid

carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.
As described previously, in preparing the compositions for oral dosage form, any of the usual pharmaceutical media can be employed. For example, in the case of oral liquid preparations such as suspensions, elixirs and solutions, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used; or in the case of oral solid preparations such as powders, capsules and tablets, carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be included. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. In addition to the common dosage forms set out above, controlled release means and/or delivery devices may also be used in administering the instant compounds and compositions.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are advantageous oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet advantageously contains from about 0.1 mg to about 500 mg of the active ingredient and each cachet or capsule advantageously containing from about 0.1 mg to about 500 mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1 mg, 1 mg, 5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, or 500 mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage, and thus should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, and dusting powder. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5

wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid, such as, for example, where the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, and preservatives (including anti-oxidants). Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to block N-type, T-type, and L-type calcium channels. Accordingly, an aspect of the invention is the treatment and prevention in mammals of conditions that are amenable to amelioration through blockage of said calcium channels by administering an effective amount of a compound of this invention. Such conditions include, for example, acute pain, chronic pain, visceral pain, inflammatory pain and neuropathic pain. These conditions may also include epilepsy, essential tremor, schizophrenia, Parkinson's disease, depression, anxiety, sleep disorders, sleep disturbances, psychosis, infertility, and sexual dysfunction. These conditions may further include cardiac arrhythmia and hypertension. The instant compounds and compositions are useful for treating and preventing the above-recited conditions, in humans and non-human mammals such as dogs and cats. It is understood that the treatment of mammals other than humans refers to the treatment of clinical conditions in non-human mammals that correlate to the above-recited conditions.

Further, as described above, the instant compounds can be utilized in combination with one or more therapeutically active compounds. In particular, the inventive compounds can be advantageously used in combination with i) opiate agonists or antagonists, ii) other calcium channel antagonists, iii) 5HT receptor agonists or antagonists, including 5-HT_{1A} agonists or

antagonists, and 5-HT_{1A} partial agonists, iv) sodium channel antagonists, v) N-methyl-D-aspartate (NMDA) receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) neurokinin receptor 1 (NK1) antagonists, viii) non-steroidal anti-inflammatory drugs (NSAID), ix) selective serotonin reuptake inhibitors (SSRI) and/or selective serotonin and norepinephrine reuptake inhibitors (SSNRI), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, xiv) norepinephrine reuptake inhibitors, xv) monoamine oxidase inhibitors (MAOIs), xvi) reversible inhibitors of monoamine oxidase (RIMAs), xvii)alpha-adrenoreceptor antagonists, xviii) atypical anti-depressants, xix) benzodiazepines, xx) corticotropin releasing factor (CRF) antagonists, xxi) neurontin (gabapentin) and xxii) pregabalin

The abbreviations used herein have the following meanings (abbreviations not shown here have their meanings as commonly used unless specifically stated otherwise): Ac (acetyl), Bn (benzyl), Boc (tertiary-butoxy carbonyl), Bop reagent (benzotriazol-1-yloxy)tris(dimethylamino)phosonium hexafluorophosphate, CAMP (cyclic adenosine-3',5'-monophosphate), DAST ((diethylamino)sulfur trifluoride), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DIBAL (diisobutylaluminum hydride), DIEA (diisopropylethyl amine), DMAP (4-(dimethylamino)pyridine), DMF (N,N-dimethylformamide), DPPF (1,1'-bisdiphenylphosphino ferrocene), EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), Et_3N (triethylamine), GST (glutathione transferase), HOBt (1-hydroxybenzotriazole), LAH (lithium aluminum hydride), Ms (methanesulfonyl; mesyl; or SO_2Me), MsO (methanesulfonate or mesylate), MCPBA (*meta*-chloro perbenzoic acid), NaHMDS (sodium hexamethyldisilazane), NBS (N-bromosuccinimide), NCS (N-chlorosuccinimide), NSAID (non-steroidal anti-inflammatory drug), PDE (Phosphodiesterase), Ph (Phenyl), r.t. or RT (room temperature), Rac (Racemic), SAM (aminosulfonyl; sulfonamide or SO_2NH_2), SPA (scintillation proximity assay), Th (2- or 3-thienyl), TFA (trifluoroacetic acid), THF (Tetrahydrofuran), Thi (Thiophenediyl), TLC (thin layer chromatography), TMEDA (N,N,N',N'-tetramethylethylenediamine), TMSI (trimethylsilyl iodide), Tr or trityl (N-triphenylmethyl), C_3H_5 (Allyl), Me (methyl), Et (ethyl), n-Pr (normal propyl), i-Pr (isopropyl), n-Bu (normal butyl), i-Butyl (isobutyl), s-Bu (secondary butyl), t-Bu (tertiary butyl), c-Pr (cyclopropyl), c-Bu (cyclobutyl), c-Pen (cyclopentyl), c-Hex (cyclohexyl).

The present compounds can be prepared according to the general Schemes provided below as well as the procedures provided in the Examples. The following Schemes and Examples further describe, but do not limit, the scope of the invention.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions: All operations were carried out at room or ambient temperature; that is, at a temperature in the range of 18-25 °C. Inert gas protection was used when reagents or intermediates were air and moisture sensitive. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30 mm Hg) with a bath temperature of up to 60 °C. The course of reactions was followed by thin layer chromatography (TLC) or by high-pressure liquid chromatography-mass spectrometry (HPLC-MS), and reaction times are given for illustration only. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz, 400 MHz or 500 MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. Broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

Assay Example 1: Fluorescent assay for Cav2.2 channels using potassium depolarization to initiate channel opening.

Human Cav2.2 channels were stably expressed in KEK293 cells along with alpha2-delta and beta subunits of voltage-gated calcium channels. An inwardly rectifying potassium channel (Kir2.3) was also expressed in these cells to allow more precise control of the cell membrane potential by extracellular potassium concentration. At low bath potassium concentration, the membrane potential is relatively negative, and is depolarized as the bath potassium concentration is raised. In this way, the bath potassium concentration can be used to regulate the voltage-dependent conformations of the channels. Compounds are incubated with cells in the presence of low (4 mM) potassium or elevated (12, 25 or 30 mM) potassium to determine the affinity for compound block of resting (closed) channels at 4 mM potassium or affinity for block of open and inactivated channels at 12, 25 or 30 mM potassium. After the

incubation period, Cav2.2 channel opening is triggered by addition of higher concentration of potassium (70 mM final concentration) to further depolarize the cell. The degree of state-dependent block can be estimated from the inhibitory potency of compounds after incubation in different potassium concentrations.

Calcium influx through Cav2.2 channels is determined using a calcium-sensitive fluorescent dye in combination with a fluorescent plate reader. Fluorescent changes were measured with either a VIPR (Aurora Instruments) or FLIPR (Molecular Devices) plate reader.

Protocol

1. Seed cells in Poly-D-Lysine Coated 96- or 384-well plate and keep in a 37°C-10%CO_2 incubator overnight
2. Remove media[1], wash cells with 0.2 ml (96-well plate) or 0.05 ml (384-well plate) Dulbecco's Phosphate Buffered Saline (D-PBS) with calcium & magnesium (Invitrogen; 14040)
3. Add 0.1 ml (96-well plate) or 0.05 ml (384-well plate) of 4 μM fluo-4 (Molecular Probes; F-14202) and 0.02% Pluronic acid (Molecular Probes; P-3000) prepared in D-PBS with calcium & magnesium (Invitrogen; 14040) supplemented with 10 mM Glucose & 10 mM Hepes/NaOH; pH 7.4
4. Incubate in the dark at 25°C for 60-70 min
5. Remove dye[2], wash cells with 0.1 ml (96-well plate) or 0.06 ml (384-well plate) of 4, 12, 25, or 30 mM Potassium Pre-polarization Buffer. (PPB)
6. Add 0.1 ml (96-well plate) or 0.03 ml (384-well plate) of 4, 12, 25, 30 mM PPB, with or without test compound
7. Incubate in the dark at 25°C for 30 min
8. Read cell plate on VIPR instrument, Excitation = 480 nm, Emission = 535 nm
9. With VIPR continuously reading, add 0.1 ml (96-well plate) or 0.03 ml (384-well plate) of Depolarization Buffer, which is 2x the final assay concentration, to the cell plate.

Assay Reagents :

4 mM K Pre-Polarization Buffer	12 mM K Pre-Polarization Buffer	25 mM K Pre-Polarization Buffer	30 mM K Pre-Polarization Buffer	140 mM K Depolarization Buffer
146 mM NaCl	138 mM NaCl	125 mM NaCl	120 mM NaCl	10 mM NaCl
4 mM KCl	12 mM KCl	25 mM KCl	30 mM KCl	140 mM KCl

0.8 mM $CaCl_2$	0.8 mM $CaCl_2$	0.8 mM $CaCl_2$	0.8 mM $CaCl_2$	0.8 mM $CaCl_2$
1.7 mM $MgCl_2$	1.7 mM $MgCl_2$	1.7 mM $MgCl_2$	1.7 mM $MgCl_2$	1.7 mM $MgCl_2$
10 mM HEPES	10 mM HEPES	10 mM HEPES	10 mM HEPES	10 mM HEPES
pH = 7.2	pH = 7.2	pH = 7.2	pH = 7.2	pH = 7.2

Assay Example 2: Electrophysiological measurement of block of Cav2.2 channels using automated electrophysiology instruments.

Block of N-type calcium channels is evaluated utilizing the IonWorks HT 384 well automated patch clamp electrophysiology device. This instrument allows synchronous recording from 384 wells (48 at a time). A single whole cell recording is made in each well. Whole cell recording is established by perfusion of the internal compartment with amphotericin B.

The voltage protocol is designed to detect use-dependent block. A 2 Hz train of depolarizations (twenty 25 ms steps to +20 mV). The experimental sequence consists of a control train (pre-compound), incubation of cells with compound for 5 minutes, followed by a second train (post-compound). Use dependent block by compounds is estimated by comparing fractional block of the first pulse in the train to block of the 20th pulse.

Protocol

Parallel patch clamp electrophysiology is performed using IonWorks HT (Molecular Devices Corp.) essentially as described by Kiss and colleagues [Kiss et al. 2003; Assay and Drug Development Technologies, 1:127-135]. Briefly, a stable HEK 293 cell line (referred to as CBK) expressing the N-type calcium channel subunits ($alpha_{1B}$, $alpha_2$-delta, $beta_{3a}$) and an inwardly rectifying potassium channel ($K_{ir}2.3$) is used to record barium current through the N-type calcium channel. Cells are grown in T75 culture plates to 60-90% confluence before use. Cells are rinsed 3x with 10ml PBS (Ca/Mg-free) followed by addition of 1.0 ml 1x trypsin to the flask. Cells are incubated at 37 ^{0}C until rounded and free from plate (usually 1-3 min). Cells are then transferred to a 15 ml conical tube with 13 ml of CBK media containing serum and antibiotics and spun at setting 2 on a table top centrifuge for 2 min. The supernatant is poured off and the pellet of cells is resuspended in external solution (in mM): 120 NaCl, 20 $BaCl_2$, 4.5 KCl, 0.5 $MgCl_2$, 10 HEPES, 10 Glucose, pH = 7.4). The concentration of cells in suspension is adjusted to achieve 1000-3000 cells per well. Cells are used immediately once they have been resuspended. The internal solution is (in mM): 100 K-Gluconate, 40 KCl, 3.2

$MgCl_2$, 3 EGTA, 5 HEPES, pH 7.3 with KOH. Perforated patch whole cell recording is achieved by added the perforating agent amphotericin B to the internal solution. A 36 mg/ml stock of amphtericn B is made fresh in dimethyl sulfoxide for each run. 166 µl of this stock is added to 50 ml of internal solution yielding a final working solution of 120 ug/ml.

Voltage protocols and the recording of membrane currents are performed using the IonWorks HT software/hardware system. Currents are sampled at 1.25 kHz and leakage subtraction is performed using a 10 mV step from the holding potential and assuming a linear leak conductance. No correction for liquid junction potentials is employed. Cells are voltage clamped at –70 mV for 10 s followed by a 20 pulse train of 25 ms steps to +20 mV at 2 Hz. After a control train, the cells are incubated with compound for 5 minutes and a second train is applied. Use dependent block by compounds is estimated by comparing fractional block of the first pulse to block of the 20th pulse. Wells with seal resistances less than 70 MOhms or less than 0.1 nA of Ba current at the test potential (+20 mV) are excluded from analysis. Current amplitudes are calculated with the IonWorks software. Relative current, percent inhibition and IC50s are calculated with a custom Excel/Sigmaplot macro.

Compounds are added to cells with a fluidics head from a 96-well compound plate. To compensate for the dilution of compound during addition, the compound plate concentration is 3x higher than the final concentration on the patch plate.

Two types of experiments are generally performed: screens and titrations. In the screening mode, 10-20 compounds are evaluated at a single concentration (usually 3 uM). The percent inhibition is calculated from the ratio of the current amplitude in the presence and absence of compound, normalized to the ratio in vehicle control wells. For generation of IC50s, a 10-point titration is performed on 2-4 compounds per patch plate. The range of concentrations tested is generally 0.001 to 20 uM. IC50s are calculated from the fits of the Hill equation to the data. The form of the Hill equation used is: Relative Current = Max-Min)/(1+(conc/IC50)^slope))+Min. Vehicle controls (dimethyl sulfoxide) and 0.3 mM $CdCl_2$ (which inhibits the channel completely) are run on each plate for normalization purposes and to define the Max and Min.

Assay Example 3: Electrophysiological measurement of block of Cav2.2 channels using whole cell voltage clamp and using PatchXpress automated electrophysiology instrument.

Block of N-type calcium channels is evaluated utilizing manual and automated (PatchXpress) patch clamp electrophysiology. Voltage protocols are designed to detect state-dependent block. Pulses (50 ms) are applied at a slow frequency (0.067 Hz) from polarized (-90 mV) or depolarized (-40 mV) holding potentials. Compounds which preferentially block inactivated/open channels over resting channels will have higher potency at -40 mV compared to -90 mV.

Protocol:

A stable HEK 293 cell line (referred to as CBK) expressing the N-type calcium channel subunits ($alpha_{1B}$, $alpha_2$-delta, $beta_{3a}$) and an inwardly rectifying potassium channel ($K_{ir}2.3$) is used to record barium current through the N-type calcium channel. Cells are grown either on poly-D-lysine coated coverglass (manual EP) or in T75 culture plates (PatchXpress). For the PatchXpress, cells are released from the flask using tryspin. In both cases, the external solution is (in mM): 120 NaCl, 20 $BaCl_2$, 4.5 KCl, 0.5 $MgCl_2$, 10 HEPES, 10 Glucose, pH 7.4 with NaOH. The internal solution is (in mM): 130 CsCl, 10 EGTA, 10 HEPES, 2 $MgCl_2$, 3 MgATP, pH 7.3 with CsOH.

Barium currents are measured by manual whole-cell patch clamp using standard techniques (Hamill et. al. Pfluegers Archiv 391:85-100 (1981)). Microelectrodes are fabricated from borosilicate glass and fire-polished. Electrode resistances are generally 2 to 4 MOhm when filled with the standard internal saline. The reference electrode is a silver-silver chloride pellet. Voltages are not corrected for the liquid junction potential between the internal and external solutions and leak is subtracted using the P/n procedure. Solutions are applied to cells by bath perfusion via gravity. The experimental chamber volume is ~0.2 ml and the perfusion rate is 0.5-2 ml/min. Flow of solution through the chamber is maintained at all times. Measurement of current amplitudes is performed with PULSEFIT software (HEKA Elektronik).

PatchXpress (Molecular Devices) is a 16-well whole-cell automated patch clamp device that operates asynchronously with fully integrated fluidics. High resistance (gigaohm) seals are achieved with 50-80% success. Capacitance and series resistance compensation is automated. No correction for liquid junction potentials is employed. Leak is subtracted using the P/n procedure. Compounds are added to cells with a pipettor from a 96-well compound plate. Voltage protocols and the recording of membrane currents are performed using the PatchXpress software/hardware system. Current amplitudes are calculated with DataXpress software.

In both manual and automated patch clamp, cells are voltage clamped at –40 mV or -90 mV and 50 ms pulses to +20 mV are applied every 15 sec (0.067 Hz). Compounds are added in escalating doses to measure % Inhibition. Percent inhibition is calculated from the ratio of the current amplitude in the presence and absence of compound. When multiple doses are achieved per cell, IC50s are calculated. The range of concentrations tested is generally 0.1 to 30 uM. IC50s are calculated from the fits of the Hill equation to the data. The form of the Hill equation used is: Relative Current = 1/(1+(conc/IC50)^slope)).

The intrinsic N-type calcium channel antagonist activity of a compound which may be used in the present invention may be determined by these assays.

In particular, the compounds of the following examples had activity in antagonizing the N-type calcium channel in the aforementioned assays, generally with an IC_{50} of less than about 10 uM. Preferred compounds within the present invention had activity in antagonizing the N-type calcium channel in the aforementioned assays with an IC_{50} of less than about 1 uM. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of N-type calcium channel activity.

Assay Example 4: Assay for Cav3.1 and Cav3.2 channels.

The T-type calcium channel blocking activity of the compounds of this invention may be readily determined using the methodology well known in the art described by Xia,et al., Assay and Drug Development Tech., 1(5), 637-645 (2003) .

In a typical experiment ion channel function from HEK 293 cells expressing the T-type channel alpha-1G, H, or I (CaV 3.1, 3.2, 3.3) is recorded to determine the activity of compounds in blocking the calcium current mediated by the T-type channel alpha-1G, H, or I (CaV 3.1, 3.2, 3.3). In this T-type calcium (Ca^{2+}) antagonist voltage-clamp assay calcium currents are elicited from the resting state of the human alpha-1G, H, or I (CaV 3.1, 3.2, 3.3) calcium channel as follows. Sequence information for T-type (Low-voltage activated) calcium channels are fully disclosed in e.g., US 5,618,720, US 5,686,241, US 5,710,250,US 5,726,035, US 5,792,846, US 5,846,757, US 5,851,824, US 5,874,236, US 5,876,958, US 6,013,474, US 6,057,114, US 6,096,514, WO 99/28342, and J. Neuroscience, *19*(6):1912–1921 (1999). Cells expressing the t-type channels were grown in H3D5 growth media which is comprised DMEM, 6 % bovine calf

serum (HYCLONE), 30 micromolar Verapamil, 200 microgram/ml Hygromycin B, 1X Penicillin/ Streptomycin. Glass pipettes are pulled to a tip diameter of 1-2 micrometer on a pipette puller. The pipettes are filled with the intracellular solution and a chloridized silver wire is inserted along its length, which is then connected to the headstage of the voltage-clamp amplifier. Trypsinization buffer was 0.05 % Trypsin, 0.53 mM EDTA. The extracellular recording solution consists of (mM): 130 mM NaCl, 4 mM KCl, 1mM MgCl2, 2mM CaCl2, 10 mM HEPES, 30 Glucose, pH 7.4. The internal solution consists of (mM): 135 mM CsMeSO4, 1 MgCl2, 10 CsCl, 5 EGTA, 10 HEPES, pH 7.4, or 135 mM CsCl, 2 MgCl2, 3 MgATP, 2 Na2ATP, 1 Na2GTP, 5 EGTA, 10 HEPES, pH 7.4. Upon insertion of the pipette tip into the bath, the series resistance is noted (acceptable range is between1-4 megaohm). The junction potential between the pipette and bath solutions is zeroed on the amplifier. The cell is then patched, the patch broken, and, after compensation for series resistance (>= 80%) , the voltage protocol is applied while recording the whole cell Ca2+ current response. Voltage protocols: (1) -80 mV holding potential every 20 seconds pulse to -20 mV for 40 msec duration; the effectiveness of the drug in inhibiting the current mediated by the channel is measured directly from measuring the reduction in peak current amplitude initiated by the voltage shift from -80 mV to -20 mV; (2). -100 mV holding potential every 15 seconds pulse to -20 mV for 40 msec duration; the effectiveness of the drug in inhibiting the current mediated by the channel is measured directly from measuring the reduction in peak current amplitude initiated by the shift in potential from -100 mV to -30 mV. The difference in block at the two holding potentials was used to determine the effect of drug at differing levels of inactivation induced by the level of resting state potential of the cells. After obtaining control baseline calcium currents, extracellular solutions containing increasing concentrations of a test compound are washed on. Once steady state inhibition at a given compound concentration is reached, a higher concentration of compound is applied. % inhibition of the peak inward control Ca2+ current during the depolarizing step to -20 mV is plotted as a function of compound concentration.

The intrinsic T-type calcium channel antagonist activity of a compound which may be used in the present invention may be determined by these assays.

In particular, the compounds of the following examples had activity in antagonizing the T-type calcium channel in the aforementioned assays, generally with an IC_{50} of less than about 10 uM. Preferred compounds within the present invention had activity in

antagonizing the T-type calcium channel in the aforementioned assays with an IC_{50} of less than about 1 uM. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of T-type calcium channel activity.

In Vivo Assay: (Rodent CFA model):

Male Sprague Dawley rats (300-400 gm) were administered 200 microl CFA (Complete Freund's Adjuvant) three days prior to the study. CFA is mycobacterium tuberculosis suspended in saline (1:1; Sigma) to form an emulsion that contains 0.5 mg mycobacterium/ml. The CFA was injected into the plantar area of the left hind paw.

Rats are fasted the night before the study only for oral administration of compounds. On the morning of test day using a Ugo Basile apparatus, 2 baseline samples are taken 1 hour apart. The rat is wrapped in a towel. Its paw is placed over a ball bearing and under the pressure device. A foot pedal is depressed to apply constant linear pressure. Pressure is stopped when the rat withdraws its paw, vocalizes, or struggles. The right paw is then tested. Rats are then dosed with compound and tested at predetermined time points.
Compounds were prepared in dimethyl sulfoxide(15%)/PEG300(60%)/Water(25%) and were dosed in a volume of 2 ml/kg.

Percent maximal possible effect (%MPE) was calculated as: (post-treatment – pre-treatment) / (pre-injury threshold – pre-treatment) x 100. The % responder is the number of rats that have a MPE.30% at any time following compound administration. The effect of treatment was determined by one-way ANOVA Repeated Measures Friedman Test with a Dunn's post test.

Methods of Synthesis:

Compounds of the present invention can be prepared according to the Schemes provided below as well as the procedures provided in the Examples. The substituents are the same as in the above Formulas except where defined otherwise or otherwise apparent to the ordinary skilled artisan.

The novel compounds of the present invention can be readily synthesized using techniques known to those skilled in the art, such as those described, for example, in Advanced Organic Chemistry, March, 5th Ed., John Wiley and Sons, New York, NY, 2001; Advanced Organic Chemistry, Carey and Sundberg, Vol. A and B, 3rd Ed., Plenum Press, Inc., New York, NY, 1990; Protective groups in Organic Synthesis, Green and Wuts, 2nd Ed., John Wiley and

Sons, New York, NY, 1991; Comprehensive Organic Transformations, Larock, VCH Publishers, Inc., New York, NY, 1988; Handbook of Heterocyclic Chemistry, Katritzky and Pozharskii, 2nd Ed., Pergamon, New York, NY, 2000 and references cited therein. Other references used for synthesizing novel compounds in the present invention include: Li, et al., *Tetrahedron Lett.*, **2004**, *45*, 4257-4260; O'Shea, et al., *J. Org. Chem.*, **2005**, *70*, 3021-3030; Ishii, et al., *J. Am. Chem. Soc.*, **2002**, *124*, 1590-1591; Vedso, et el., *Org. Lett.*, **2001**, *3*, 1435-1437; Hwu et el., *Tetrahedron Lett.*, **1996**, *37*, 2035-2038; Buckwald et el, *Tetrahedron*, **2004**, *60*, 7397-7403; Dessard et el., *Org. Proc. Res. Dev.*, **2001**, *5*, 572-574; Beaulieu et el, *Tetrahedron lett.*, **2004**, *45*, 3233-3236; Schlosser et el., *Tetrahedron*, **2004**, *60*, 11869-11874; Meyers et el, *Tetrahedron*, **1984**, *41*, 837-860; Campos et el., *J. Org. Chem.*, **2005**, *70*, 268-274. The starting materials for the present compounds may be prepared using standard synthetic transformations of chemical precursors that are readily available from commercial sources, including Aldrich Chemical Co. (Milwaukee, WI); Sigma Chemical Co. (St. Louis, MO); Lancaster Synthesis (Windham, N.H.); Ryan Scientific (Columbia, S. C.); Maybridge (Cornwall, UK); Matrix Scientific (Columbia, S. C.); Arcos, (Pittsburgh, PA) and Trans World Chemicals (Rockville, MD).

The procedures described herein for synthesizing the compounds may include one or more steps of protecting group manipulations and of purification, such as, re-crystallization, distillation, column chromatography, flash chromatography, thin-layer chromatography (TLC), radial chromatography and high-pressure chromatography (HPLC). The products can be characterized using various techniques well known in the chemical arts, including proton and carbon-13 nuclear magnetic resonance (^{1}H and ^{13}C NMR), infrared and ultraviolet spectroscopy (IR and UV), X-ray crystallography, elemental analysis and HPLC and mass spectrometry (HPLC-MS). Methods of protecting group manipulation, purification, structure identification and quantification are well known to one skilled in the art of chemical synthesis.

Appropriate solvents are those which will at least partially dissolve one or all of the reactants and will not adversely interact with either the reactants or the product. Suitable solvents are aromatic hydrocarbons (e.g, toluene, xylenes), halogenated solvents (e.g, methylene chloride, chloroform, carbontetrachloride, chlorobenzenes), ethers (e.g, diethyl ether, diisopropylether, tert-butyl methyl ether, diglyme, tetrahydrofuran, dioxane, anisole), nitriles (e.g, acetonitrile, propionitrile), ketones (e.g, 2-butanone, dithyl ketone, tert-butyl methyl ketone), alcohols (e.g, methanol, ethanol, n-propanol, iso-propanol, n-butanol, t-butanol), N,N-dimethyl

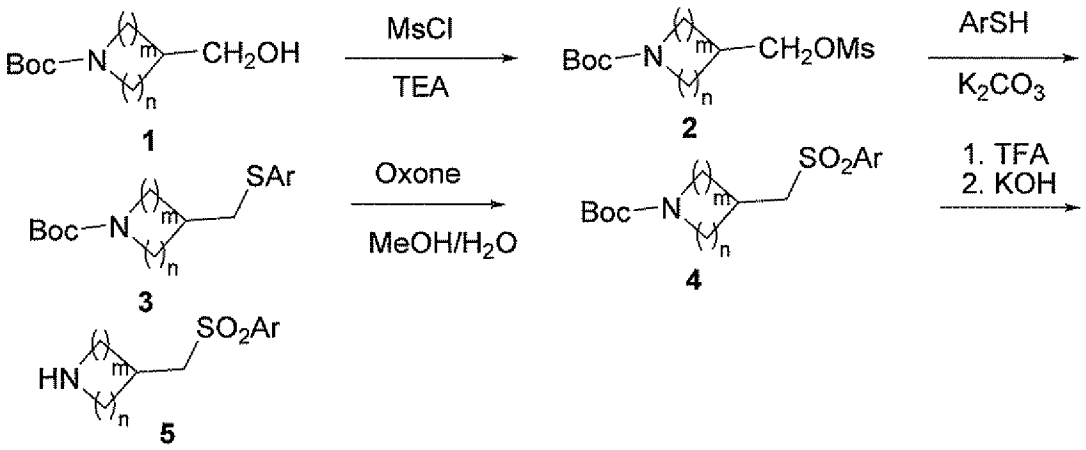
formamide (DMF), dimethylsulfoxide (DMSO) and water. Mixtures of two or more solvents can also be used. Suitable bases are, generally, alkali metal hydroxides, alkaline earth metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, and calcium hydroxide; alkali metal hydrides and alkaline earth metal hydrides such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal amides such as lithium amide, sodium amide and potassium amide; alkali metal carbonates and alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, cesium carbonate, sodium hydrogen carbonate, and cesium hydrogen carbonate; alkali metal alkoxides and alkaline earth metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and magnesium ethoxide; alkali metal alkyls such as methyllithium, n-butyllithium, sec-butyllithium, t-bultyllithium, phenyllithium, alkyl magnaesium halides, organic bases such as trimethylamine, triethylamine, triisopropylamine, N,N-diisopropylethyl amine, piperidine, N-methyl piperidine, morpholine, N-methyl morpholine, pyridine, collidines, lutidines, and 4-dimethylaminopyridine; and bicyclic amines such as DBU and DABCO.

It is understood that the functional groups present in compounds described in the Schemes below can be further manipulated, when appropriate, using the standard functional group transformation techniques available to those skilled in the art, to provide desired compounds described in this invention.

It is also understood that compounds listed in the Schemes and Tables below that contain one or more stereocenters may be prepared as single enantiomers or diastereomers, or as mixtures containing two or more enantiomers or diastereomers in any proportion.

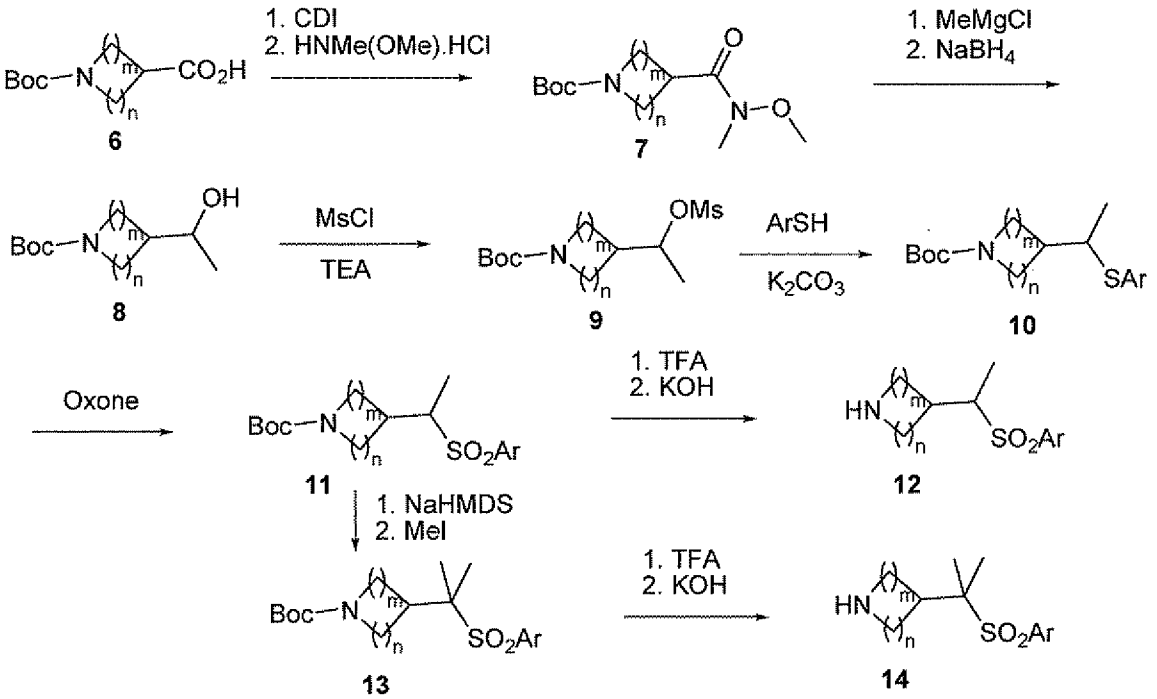
Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

Scheme 1



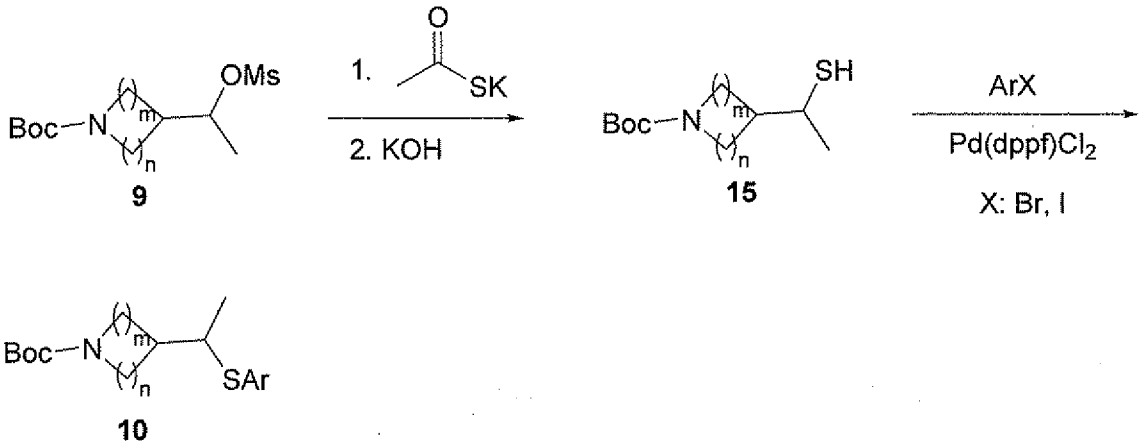
Amine intermediates **5** were synthesized as shown in Scheme 1. Commercially available Boc protected amino alcohols **1** such as *tert*-butyl 3-(hydroxymethyl)azetidine-1-carboxylate (m, n = 1), *tert*-butyl 3-(hydroxymethyl)pyrrolidine-1-carboxylate (m = 1, n = 2) and *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate (m, n = 2) were converted to mesylates **2** by treatment of methanesulfonyl chloride or methanesulfonic anhydride and an appropriate base such as triethylamine. The resulted mesylates **2** can be displaced by selected thiols in present of a suitable base such as K_2CO_3 to give desired thioether products **3**, which were oxidized with Oxone™ or *meta* chloroperbenzoic acid (MCPBA) to give sulfone products **4**. Deprotection of the Boc group with trifluoroacetic acid gave desired aminesulfone products **5**.

Scheme 2



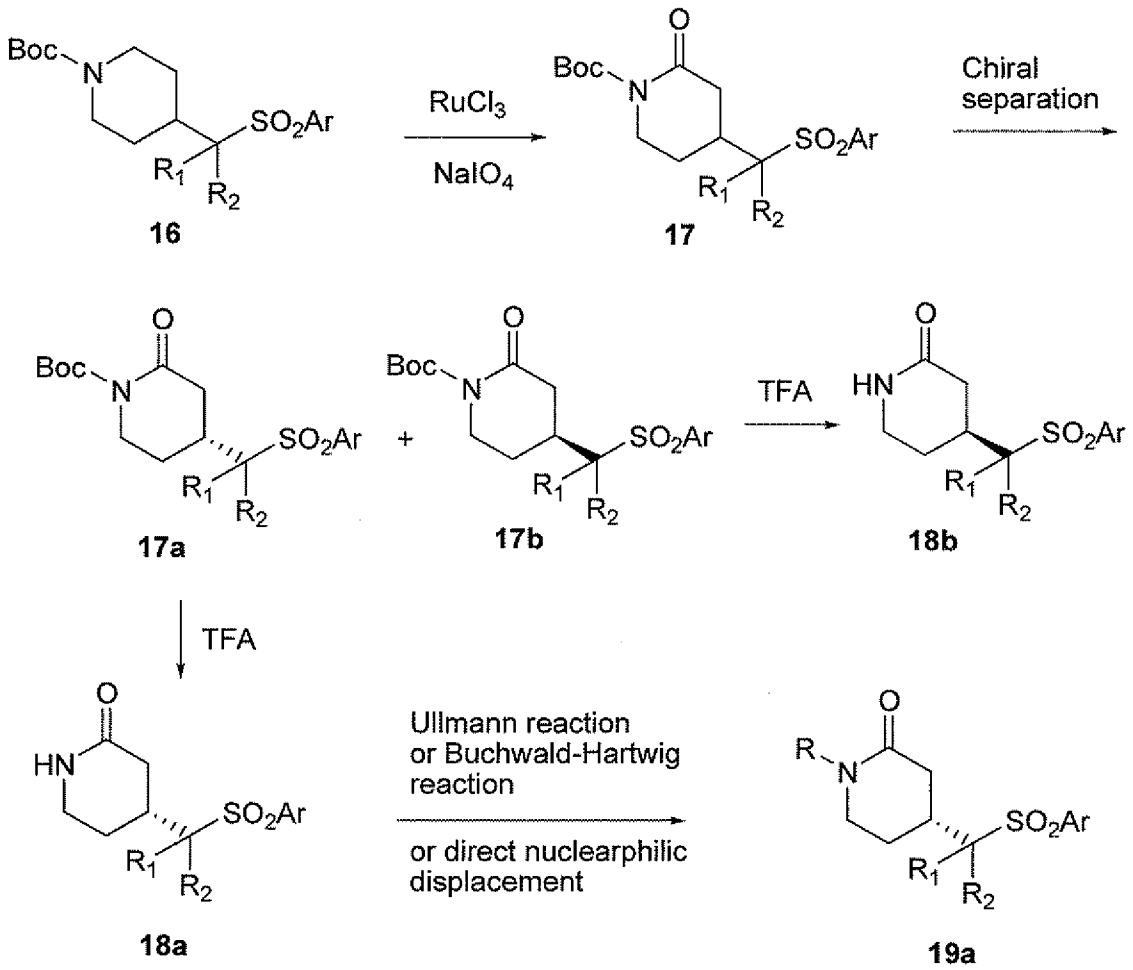
To introduce substitutions such as methyl or gem dimethyl groups at α position to the sulfone group, Boc protected amino acids **6** such as 1-(*tert*-butoxycarbonyl)azetidine-3-carboxylic acid (m, n = 1), 1-(*tert*-butoxycarbonyl)pyrrolidine-3-carboxylic acid (m =1, n = 2) and 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (m, n = 2) were converted to their corresponding Weinreb amides **7** using procedures known to those of ordinary skill in the art. Weinreb amides **7** were then treated with methyl Grignard reagent to give methyl ketone intermediates which were sequentially reduced to alcohols **8** with $NaBH_4$. Alcohol compounds **8** were converted to mesylates **9** by treatment of methanesulfonyl chloride or methanesulfonic anhydride and an appropriate base such as triethylamine. The resulted mesylates **9** can be displaced by selected thiols in present of a suitable base such as K_2CO_3 to give desired thioether products **10**, which were oxidized with Oxone™ or MCPBA to give sulfone products **11**. Deprotection of the Boc group with trifluroacetic acid gave desired amine products **12**. To synthesize gem dimethyl compounds **13**, sulfone compounds **11** were treated with sodium bis(trimethylsilyl)amide (NaHMDS) to generate sulfone anions which were alkylated by addition of iodomethane (MeI). Boc protecting group was then removed by treating with trifluoroacetic acid to give desired aminesulfone compounds **14**.

Scheme 3



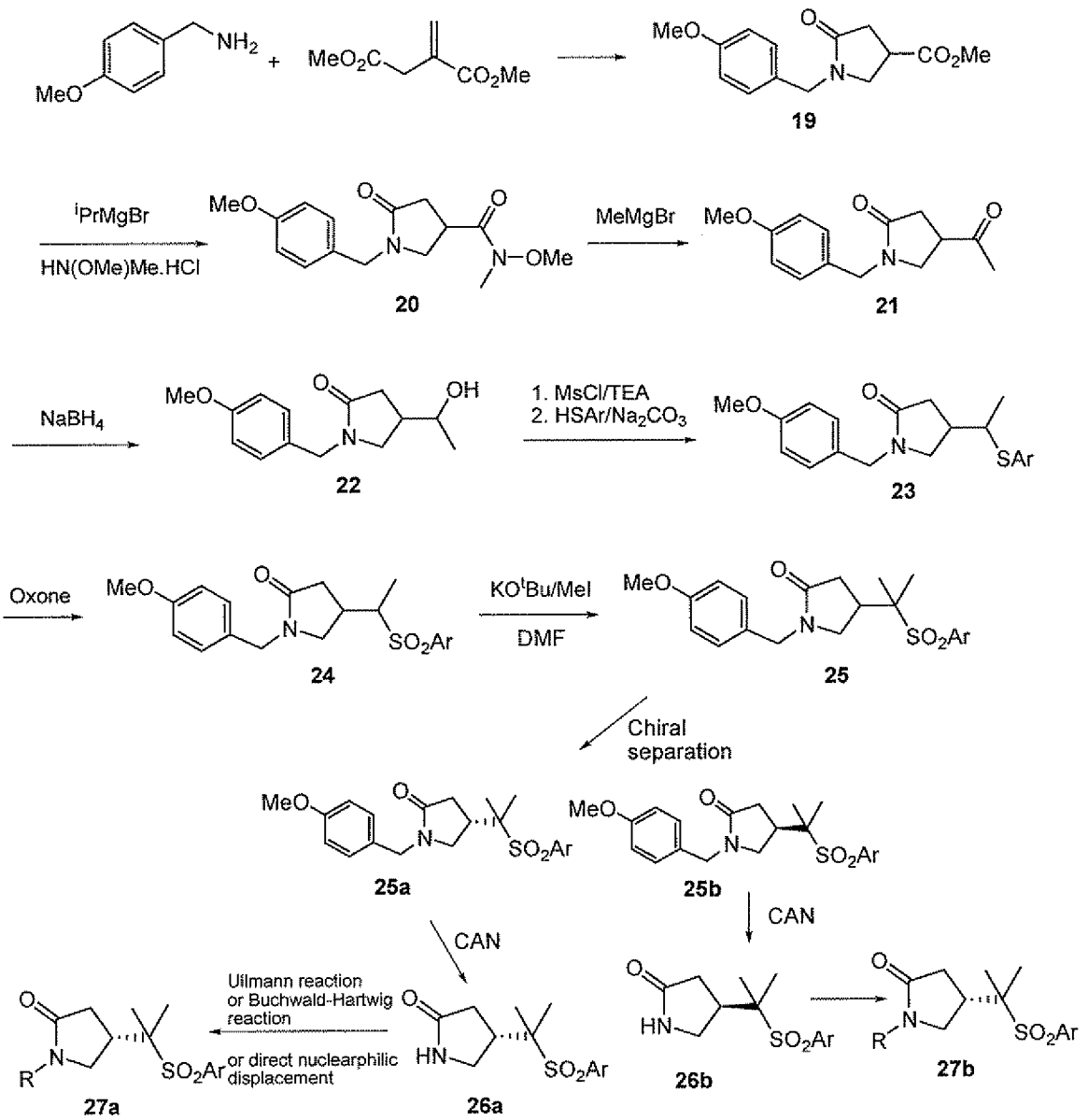
Alternatively, thioethers such compounds **10** can be synthesized following Scheme 3. Mesylates **9** were treated with potassium ethanethiolate to give thioesters which were hydrolyzed to give thio compounds **15**. Palladium mediated coupling reaction between **15** and selected aryl halides gave desired thioethers **10**. Thioethers **10** can be converted to amines **12** and **14** following the reactions outlined in Scheme 2.

Scheme 4



Boc protected piperidine compound **16** (Scheme 4) can be selectively oxidized to piperidinone compound **17** with $NaIO_4$ and catalytic amount of $RuCl_3$. Compound **17** , a mixture of a pair of enantiomers, can be readily separated on chiral column to give **17a** and **17b**. Removal of Boc protecting group with trifluroacetic acid at ambient temperature can provide enontiomarically pure piperidinone **18a** and **18b**. The lactam nitrogen in **18a** and **18b** can be readily substituted with groups such as alkyl, aromatic and hetero aromatic moieties by either a direct nucleophilic displacement reaction or utilizing Ullmann or Buchwald-Hartwig reaction conditions (Hartwig et el., *J. Org. Chem.*, **2003**, *68*, 2861-2873; Buchwald et el., *Org. Lett.*, **2006**, 2779-2782), as outlined in Scheme 4.

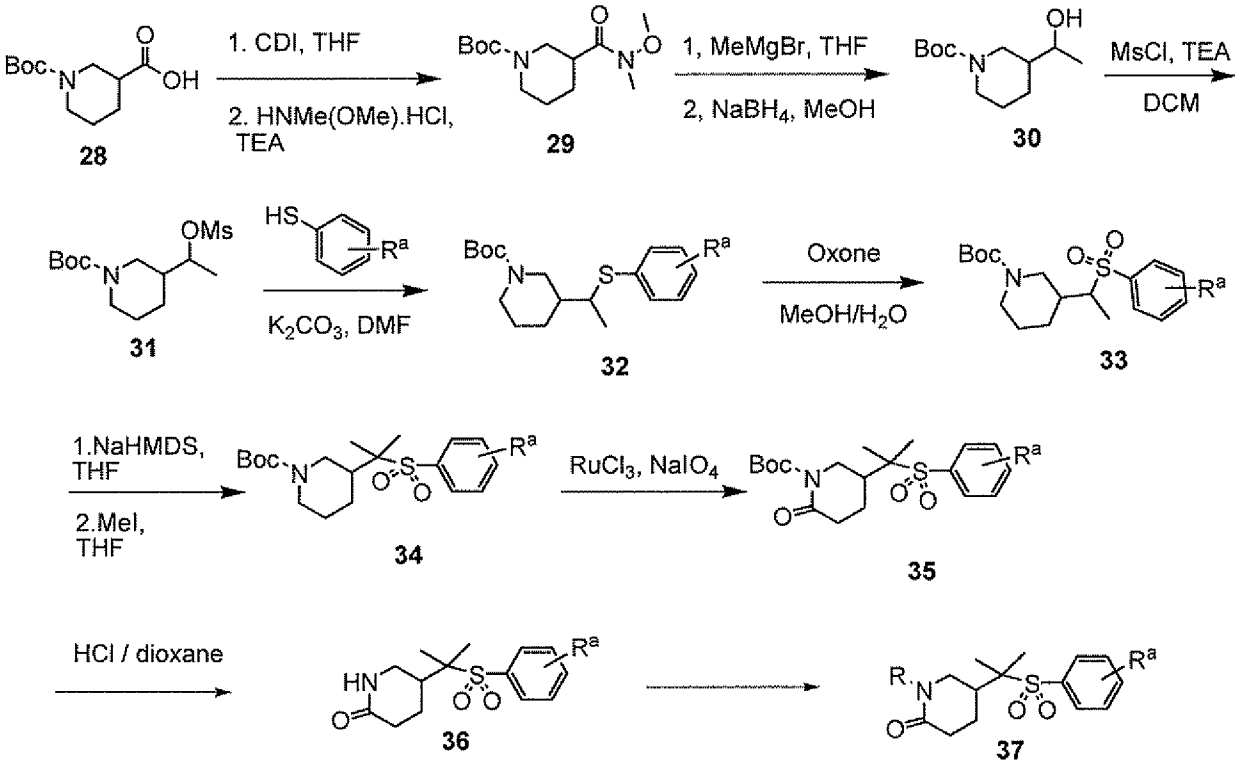
Scheme 5



Methyl 1-(4-methoxybenzyl)-5-oxopyrrolidine-3-carboxylate (**19**), synthesized according to a known procedure from 4-methoxybenzylamine and dimethyl itaconate (Amri et el., *Tetrahedron*, **1999**, **55**, 3949-3958), can be easily converted into the corresponding Weinreb amide **20** using a procedure developed by Merck group (Williams *et al.*, *Tetrahedron Lett.*, **1995**, *36*, 5461-5464). Treatment of the amide **20** with methyl Grignard reagent provides

the methyl ketone **21** which can be reduced with $NaBH_4$ to provide alcohol **22**. The mesylate intermediated of **22** obtained, as outlined in Scheme 5, can be reacted with selected thiols in presence of a suitable base, such as K_2CO_3, to produce the desired thioether **23**. Oxidation of **23** with Oxone™ or MCPBA provides sulfone **24**, which upon treatment with potassium tert-butoxide and iodomethane produces racemic mixture of **25**. Separation of the enantiomers **25a** and **25b** by chiral chromatography followed by deprotection of the PMB group with CAN can provide the key pyrrolidinone products **26a** and **26b**. Further elaboration of **26a** and **26b**, as outlined in Scheme 5, using the known procedures described in the literature (Hartwig et el., *J. Org. Chem.*, **2003**, *68*, 2861-2873; Buchwald et el., *Org. Lett.*, **2006**, 2779-2782) can provide the products **27a** and **27b**.

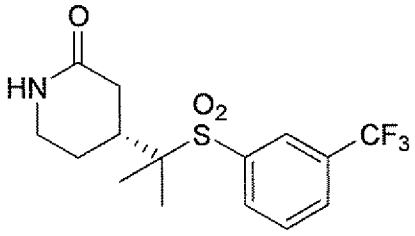
Scheme 6



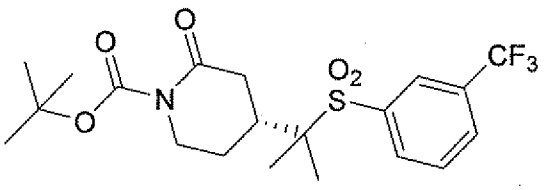
The isomeric piperid-3-ones **37** can be prepared as outlined in Scheme 6.

EXAMPLE 1

(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one



Step 1: *tert*-butyl (4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidine-1-carboxylate

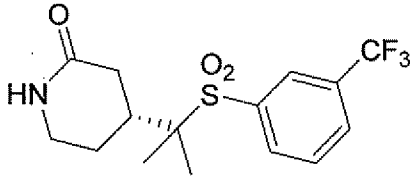


To a 500 ml round bottom flask were added *tert*-butyl 4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidine-1-carboxylate (11.2 g, 25.7 mmol), sodium periodate (13.75 g, 64.3 mmol), ruthenium chloride (1.07 g, 5.14 mmol), 100 ml water and 100 ml EtOAc. The resulting reaction mixture was stirred vigorously at ambient temperature for 16 hours. The reaction mixture turned black. It was filtered through a pad of celite. Layers were separated from the filtrate. Organic portion was dried over sodium sulfate, filtered and concentrated. Crude product was purified on silica gel column eluted with 1:2 to 1:1 EtOAc/hexane to give 11 g desired product. The pair of enantiomers were separated on ChiralPak AD column eluted with 15% MeOH/CO_2 at 100 bar to give 4.2 g title compound and 3.8 g *S*-enantiomer both as crystalline solid. The title compound has shorter retention time than the *S*-enantiomer (4.7 min and 6.6 min, ChiralPak AD-H, 4.6x250mm, 15%MeOH/CO_2, 2.1 ml/min, 100 bar, 40 °C).

^{1}H-NMR ($CDCl_3$): δ8.15 (s, 1H), 8.09 (d, J = 8 Hz, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.78 (t, J = 7.9, 1H), 3.9 (m, 1H), 3.5 (m, 1H), 2.8 (m, 1H), 2.5 (m, 3H), 1.8 (m, 1H), 1.55 (s, 9H), 1.33 (s, 3H), 1.24 (s, 3H).

Mass Spectra (m/e): 472 (M+23, M+Na^+).

Step 2: (4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one

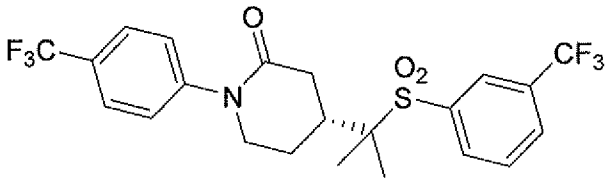


To a 25 ml round bottom flask were added *tert*-butyl (4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidine-1-carboxylate (1.2 g, 2.7 mmol), TFA (3.0 g, 26.7 mmol) and 1 ml dichloromethane. The resulting reaction solution was stirred at room temperature for 30 minutes. Volatiles were removed. Residue was partitioned between 50 ml EtOAc and 50 ml 10% KOH. Organics were washed with 30 ml brine, dried over sodium sulfate, filtered and concentrated to give 0.8 g title compound as crystalline solid.

^{1}H-NMR (CD_3OD): δ8.17 (d, J = 7.8 Hz,1H), 8.12 (s,1H), 8.09 (d, J = 8.1 Hz, 1H), 7.89 (t, J = 7.9, 1H), 3.4 (m, 1H), 3.2 (m, 1H), 2.6 (m, 1H), 2.4 (m, 3H), 1.6 (m, 1H), 1.31 (s, 3H), 1.26 (s, 3H).
Mass Spectra (m/e): 350 (M+1).

EXAMPLE 2

(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]piperidin-2-one

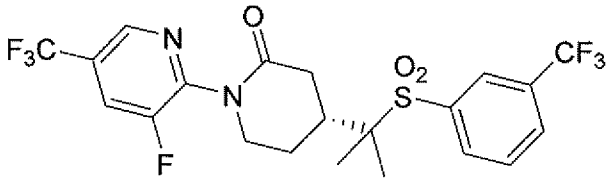


To a 10 ml microwave tube charged with (4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one (93 mg, 0.27 mmol), potassium carbonate (110 mg, 0.80 mmol), CuI (51 mg, 0.266 mmol), *p*-iodobenzotrifluoride (109 mg, 0.40 mmol), *N,N'*-dimethylethylenediamine (57 µl, 0.53 mmol) and 5 ml toluene. The tube was flushed with nitrogen gas. It was sealed and heated at 130 °C for 6 hrs. After cooling to room temperature, reaction mixture was diluted with 20 ml EtOAc, washed sequentially with 30 ml water, 30ml 5% KOH, 30 ml 1N HCl. Organics were dried over sodium sulfate, filtered and concentrated. Residue was purified on reverse phase column eluted with water/acetonitrile gradient solvent to give 113 mg title compound as white fluffy solid after lyophililzing.

^{1}H-NMR ($CDCl_3$): δ; 8.17 (s, 1H), 8.12 (d, J = 8.0 Hz,1H), 7.99 (d, J = 8.0 Hz,1H),7.79 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 3.85 (m, 1H), 3.7 (m, 1H), 2.8 (m, 3H), 2.55 (m, 1H), 2.0 (m, 1H), 1.39 (s, 3H), 1.28 (s, 3H).
Mass Spectra (m/e): 494 (M+1).

EXAMPLE 3

(4*R*)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one

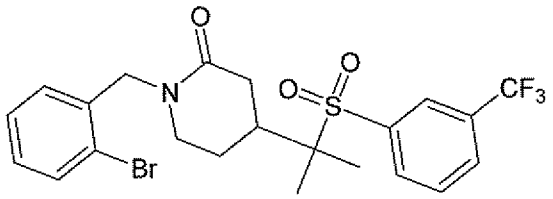


To a 10 ml vial contains with (4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one (70 mg, 0.20 mmol) and 2 ml THF was added NaHMDS THF solution (1M, 0.21 ml, 0.21 mmol) via a syringe at – 78 °C. The resulting reaction mixture was stirred at – 78 °C for 5 min. A THF solution of 2,3-difluoro-5-(trifluoromethyl)pyridine (40.4 mg in 0.5 ml THF, 0.22 mmol) was added via syringe. The resulting reaction mixture was allowed to warm up to room temperture and stirred for another 30 min. Volatiles were removed. Residue was diluted with water and DMF. It was purified on reverse phase column eluted with water/acetonitrile gradient solvent to give 74 mg title compound as fluffy white solid.

^{1}H-NMR ($CDCl_3$): δ; 8.60 (s, 1H), 8.19 (s, 1H), 8.13 (d, J = 7.8 Hz,1H), 7.99 (d, J = 7.7 Hz,1H), 7.80 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 4.0 (m, 1H), 3.85 (m, 1H), 2.8 (m, 3H), 2.6 (m, 1H), 2.0 (m, 1H), 1.41 (s, 3H), 1.31 (s, 3H).
Mass Spectra (m/e): 513 (M+1).

EXAMPLE 4

1-(2-bromobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one

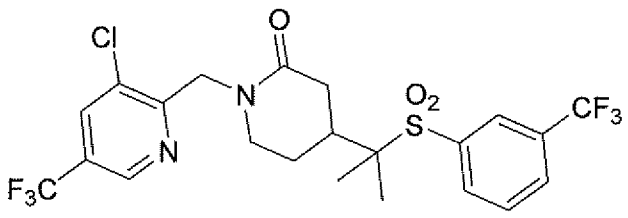


A solution of 4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one (0.5 g, 1.4 mmol) in DMF(8 mL) was added NaH (0.17 g, 4.2 mmol) at 0 ℃. The mixture was stirred at room temperature for 0.5 hour, then 1-bromo-2-(bromomethyl)benzene (0.7 g, 2.8 mmol) was added drop wise. The mixture was stirred another 2 hours. It was extracted by EtOAc, washed with brine and dried over Na_2SO_4, filtered, concentrated and purified by silica gel chromatography to give title compound (0.35 g, 48%).

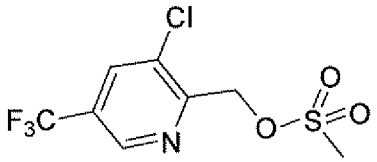
^{1}HNMR ($CDCl_3$) δ: 8.10(s, 1H), 8.05(d, *J*=7.8Hz, 1H), 7.88(d, *J*=7.8Hz, 1H), 7.68(t, *J*=7.8Hz, 1H), 7.50(d, *J*=7.8Hz, 1H), 7.05~7.30(m, 3H), 4.55~4.80(m, 4H), 3.18~3.30(m, 2H), 2.20~2.60 (m, 4H), 1.60~1.70 (m, 1H), 1.30 (s, 3H), 1.20 (s, 3H).

EXAMPLE 5

1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one



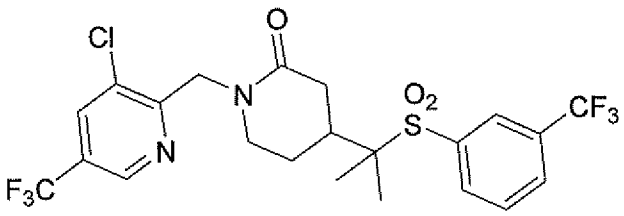
Step 1: [3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl methanesulfonate



To a 10 ml vial were added [3-chloro-5-(trifluoromethyl)pyridin-2-yl]methanol (0.30 g, 1.42 mmol), TEA (0.59 ml, 4.3 mmol) and 5 ml dichloromethane. Methanesulfonyl chloride was added at 0 °C. The resulting reaction mixture was stirred at room temperature for 20 minutes. It was diluted with 20 ml EtOAc, washed with 30 ml water. Organics were dried over sodium sulfate, filtered and concentrated. Residue was purified on silica gel column eluted with 4:1 EtOAc/hexane to give 0.38 g title compound.

^{1}H-NMR ($CDCl_3$): δ: 8.84 (s, 1H), 8.03 (s, 1H), 5.55 (s, 2H), 3.20 (s, 3H).

Step 2: 1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one

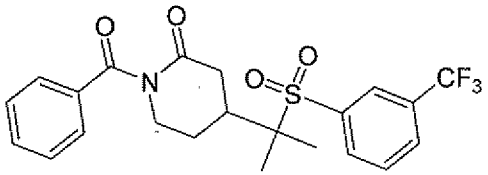


To a 10 ml vial contains 2,2,6,6-tetramethylpiperidine (51 µl, 0.30 mmol) and 2 ml THF was added a hexane solution of nBuLi (2.5 M, 0.114 ml, 0.29 mmol). After stirring at room temperature for 5 min, it was cooled to -78 °C. A THF solution of 4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one (100 mg, 0.286 mmol, 1 ml THF) was added via a syringe. After stirring for 5 min, a THF solution of [3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl methanesulfonate (91 mg, 0.315 mmol, in 1 ml THF) was added via a syringe. Reaction mixture was allowed to warm up to room temperature. Volatiles were removed. Residue was diluted with DMF and water. It was purified on reverse phase column eluted with water/acetonitrile gradient solvent to give 60 mg title compound.

^{1}H-NMR ($CDCl_3$): δ; 8.72 (s, 1H), 8.16 (s, 1H), 8.12 (d, J = 7.8 Hz,1H), 7.99 (d, J = 8.0 Hz,1H), 7.95 (s, 1H), 7.79 (t, J = 7.8 Hz, 1H), 4.97 (d, J = 17.1 Hz, 1H), 4.81 (d, J = 17.0 Hz, 1H), 3.6 (m, 1H), 3.45 (m, 1H), 2.7 (m, 3H), 2.5 (m, 1H), 1.9 (m, 1H), 1.39 (s, 3H), 1.27 (s, 3H).
Mass Spectra (m/e): 543 (M+1).

EXAMPLE 6

1-benzoyl-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one

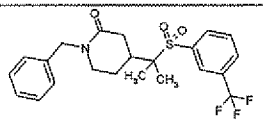
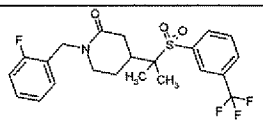
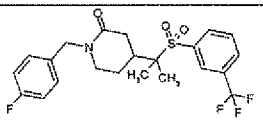
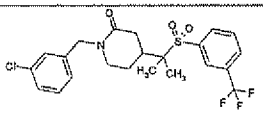
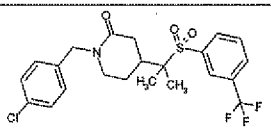
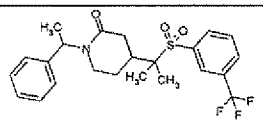
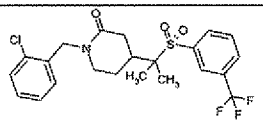
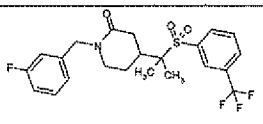


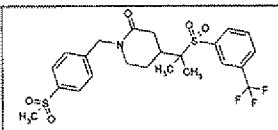
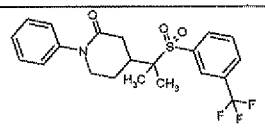
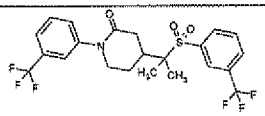
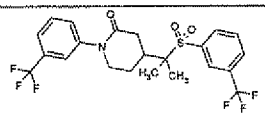
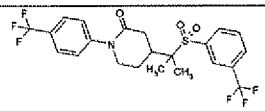
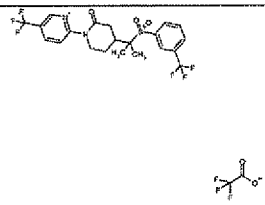
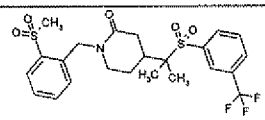
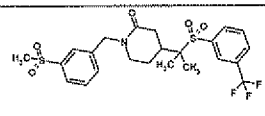
To a solution of 4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one (0.4 g, 1.15 mmol) in THF(10 mL) was added TEA (0.46 g, 4.6 mmol) and benzoyl chloride (0.32 g, 2.3 mmol), and the mixture was stirred at room temperature for 2 hours. Then water (10 mL) was added and the mixture was extracted with EtOAc (10 mL×3). The combined organic layers were washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative HPLC under neutral condition to give the title compound (23 mg, 5 %).

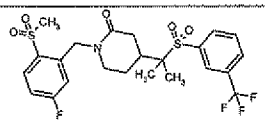
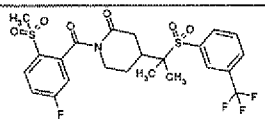
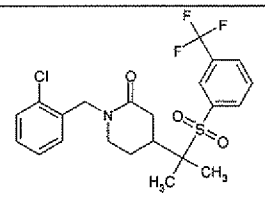
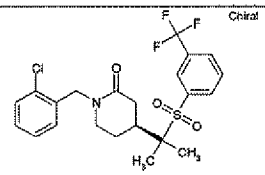
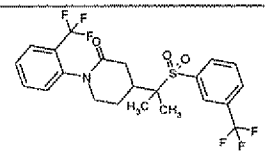
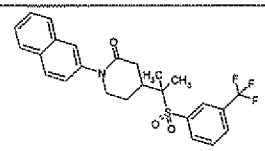
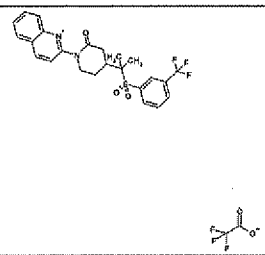
^{1}HNMR ($CDCl_3$) δ: 8.05~8.15 (m, 2H), 7.90~8.00 (m, 1H), 7.70~7.80 (m, 1H), 7.40~7.60 (m, 5H), 4.01~4.10 (m, 1H), 3.55~3.70 (m, 1H), 2.80~2.95 (m, 1H), 2.55~2.70 (m, 3H), 1.75~1.95 (m, 1H), 1.35 (s, 3H), 1.24 (s, 3H).
MS (M+1): 454.

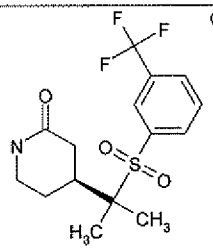
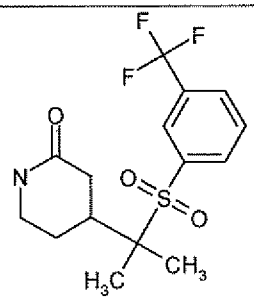
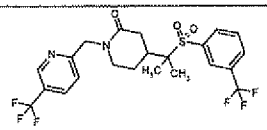
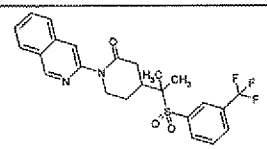
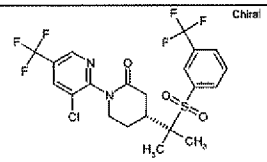
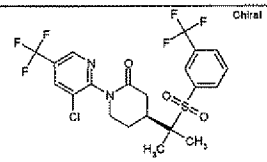
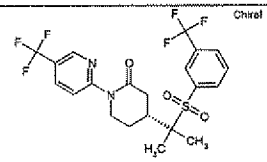
Using the procedures described in EXAMPLES 1 – 7 with the appropriate modifications, reagents and substrates the following compounds of the current invention were prepared.

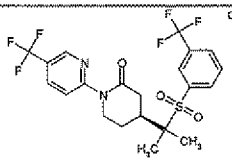
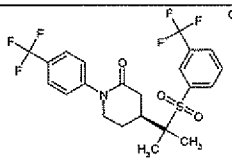
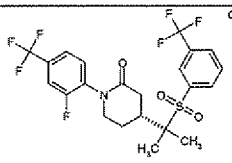
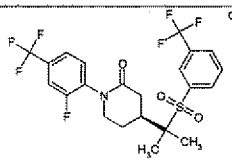
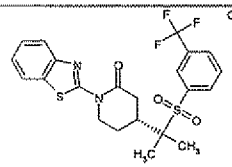
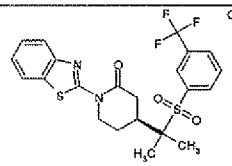
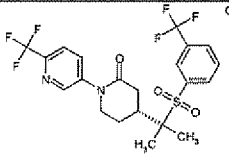
TABLE 1

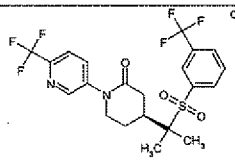
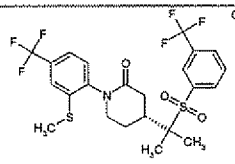
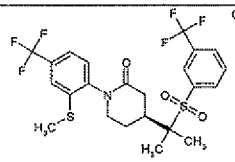
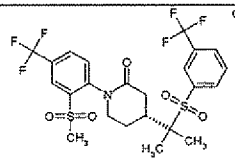
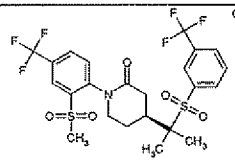
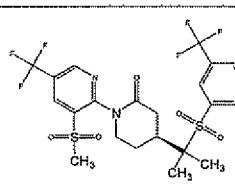
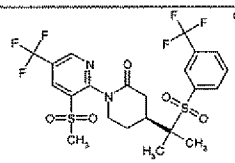
EXAMPLE #	STRUCTURE	CHEMICAL NAME	MASS SPECTRAL DATA m/e (M+H)
7		1-benzyl-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	440
8		1-(2-fluorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	458
9		1-(4-fluorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	458
10		1-(3-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	474
11		1-(4-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	474
12		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(1-phenylethyl)piperidin-2-one	454
13		1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	474
14		1-(3-fluorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	458

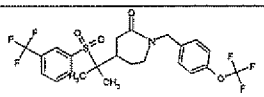
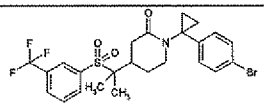
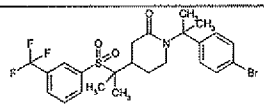
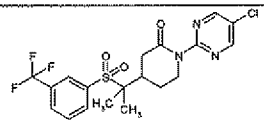
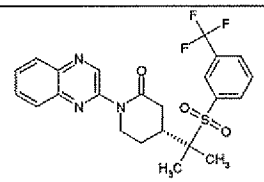
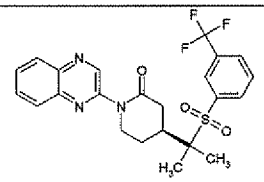
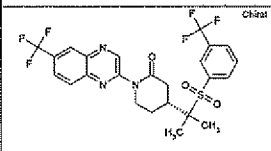
15		1-[4-(methylsulfonyl)benzyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	518
16		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-phenylpiperidin-2-one	426
17		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)phenyl]piperidin-2-one	494
18		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)phenyl]piperidin-2-one	494
19		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]piperidin-2-one	494
20		2-[4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)pyridinium trifluoroacetate	495
21		1-[2-(methylsulfonyl)benzyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	518
22		1-[3-(methylsulfonyl)benzyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	518

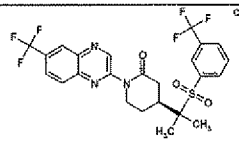
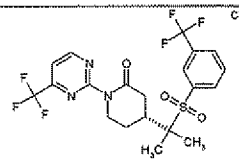
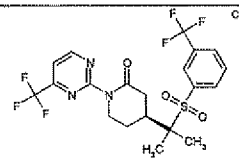
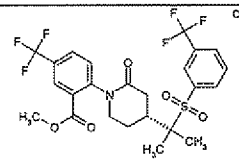
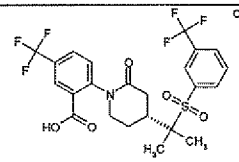
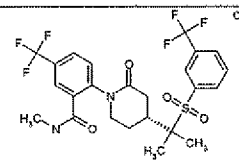
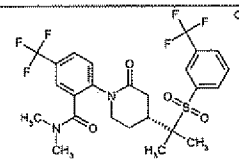
23		1-[5-fluoro-2-(methylsulfonyl)benzyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	536
24		1-[5-fluoro-2-(methylsulfonyl)benzoyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	550
25		1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	475
26		(4*S*)-1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	475
27		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)phenyl]piperidin-2-one	494
28		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(2-naphthyl)piperidin-2-one	477
29		2-[4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]quinolinium trifluoroacetate	477

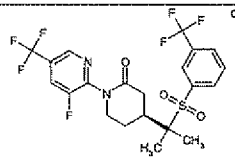
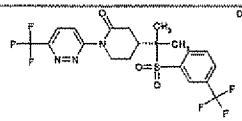
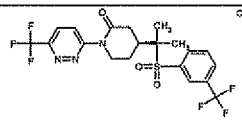
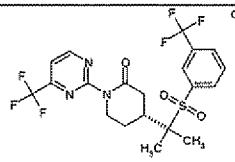
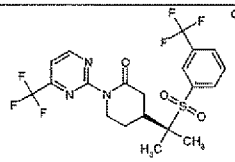
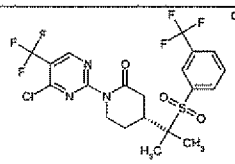
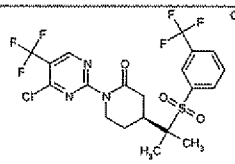
30		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	350
31		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	350
32		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-{[5-(trifluoromethyl)pyridin-2-yl]methyl}piperidin-2-one	509
33		1-isoquinolin-3-yl-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	477
34		(4*R*)-1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	529
35		(4*S*)-1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	529
36		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495

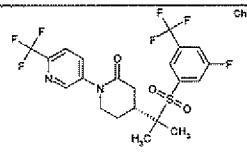
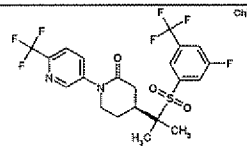
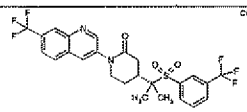
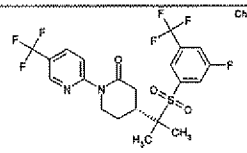
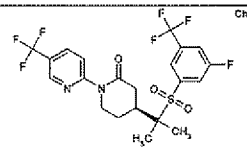
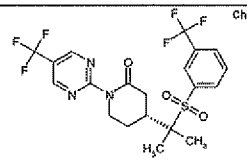
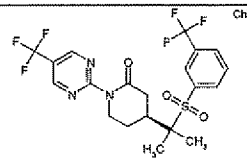
37		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495
38		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]piperidin-2-one	494
39		(4*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	512
40		(4*S*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	512
41		(4*R*)-1-(1,3-benzothiazol-2-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	483
42		(4*S*)-1-(1,3-benzothiazol-2-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	483
43		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	495

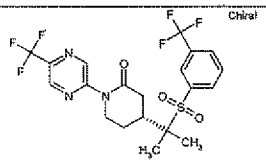
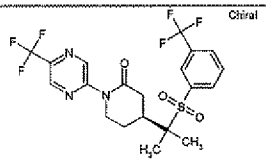
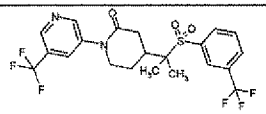
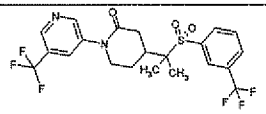
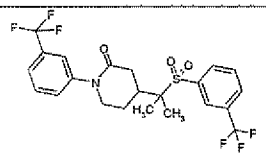
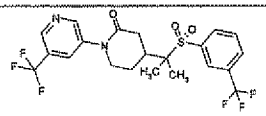
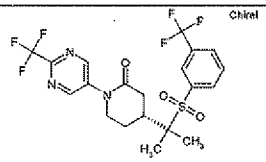
44		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	495
45		(4*R*)-1-[2-(methylthio)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	540
46		(4*S*)-1-[2-(methylthio)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	540
47		(4*R*)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	572
48		(4*S*)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	572
49		(4*R*)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	573
50		(4*S*)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	573

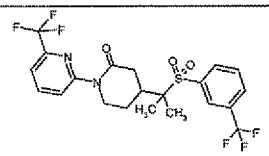
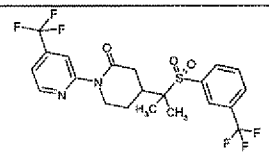
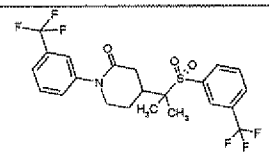
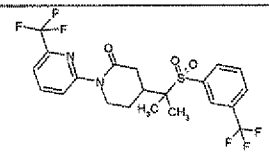
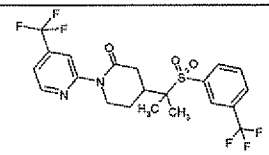
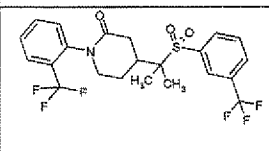
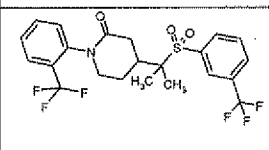
51		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethoxy)benzyl]piperidin-2-one	524
52		1-[1-(4-bromophenyl)cyclopropyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	545
53		1-[1-(4-bromophenyl)-1-methylethyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	547
54		1-(5-chloropyrimidin-2-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	462
55		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-quinoxalin-2-ylpiperidin-2-one	478
56		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-quinoxalin-2-ylpiperidin-2-one	478
57		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)quinoxalin-2-yl]piperidin-2-one	546

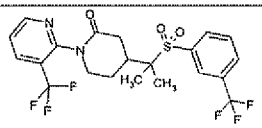
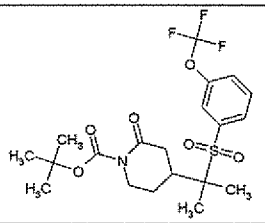
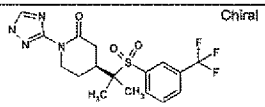
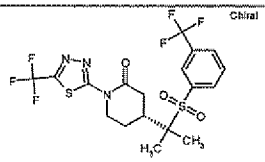
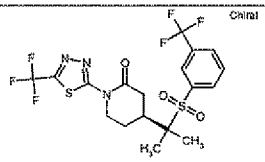
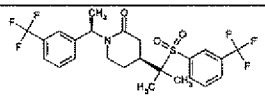
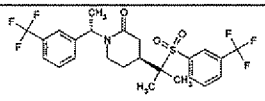
58		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)quinoxalin-2-yl]piperidin-2-one	546
59		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one	496
60		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one	496
61		methyl 2-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)benzoate	552
62		2-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)benzoic acid	538
63		*N*-methyl-2-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)benzamide	551
64		*N*,*N*-dimethyl-2-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)benzamide	565

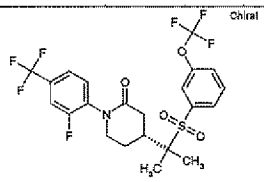
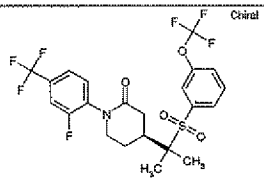
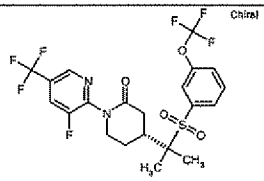
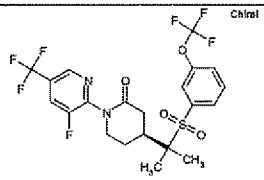
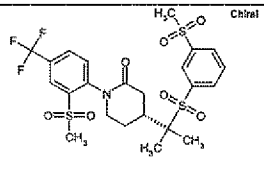
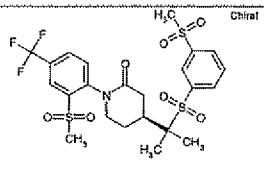
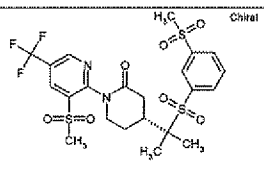
65		(4*S*)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	513
66		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]piperidin-2-one	496
67		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]piperidin-2-one	496
68		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one	496
69		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one	496
70		(4*R*)-1-[4-chloro-5-(trifluoromethyl)pyrimidin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	530
71		(4*S*)-1-[4-chloro-5-(trifluoromethyl)pyrimidin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	530

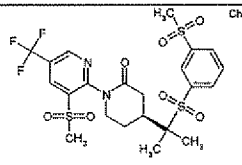
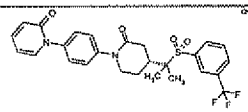
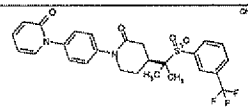
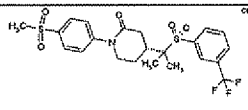
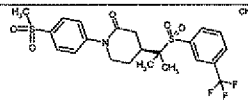
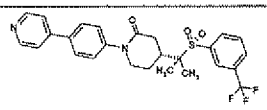
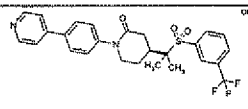
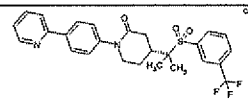
72		(4*R*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	513
73		(4*S*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	513
74		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[7-(trifluoromethyl)quinolin-3-yl]piperidin-2-one	545
75		(4*R*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	513
76		(4*S*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	513
77		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one	496
78		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one	496

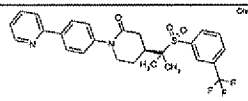
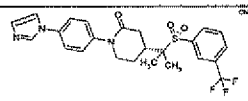
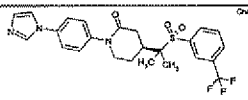
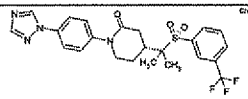
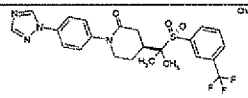
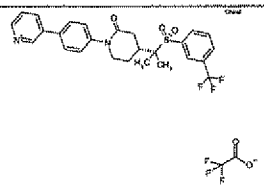
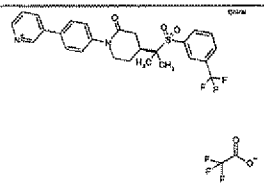
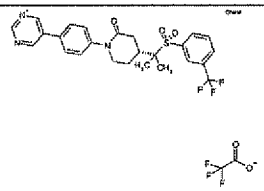
79		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyrazin-2-yl]piperidin-2-one	496
80		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyrazin-2-yl]piperidin-2-one	496
81		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	495
82		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	495
83		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)phenyl]piperidin-2-one	494
84		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	495
85		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]piperidin-2-one	496

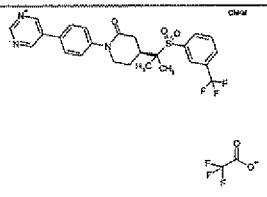
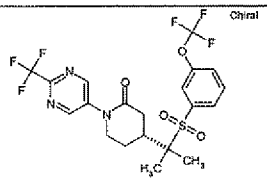
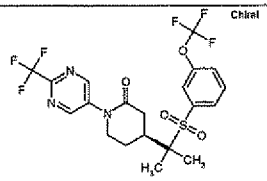
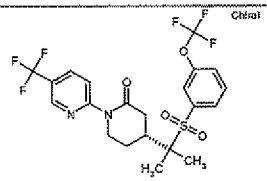
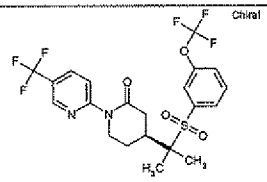
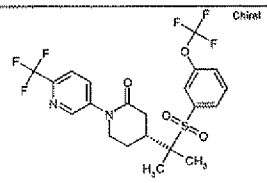
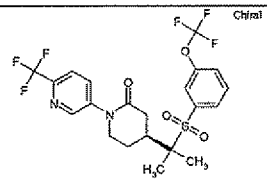
86		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495
87		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495
88		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)phenyl]piperidin-2-one	494
89		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495
90		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495
91		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)phenyl]piperidin-2-one	494
92		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)phenyl]piperidin-2-one	494

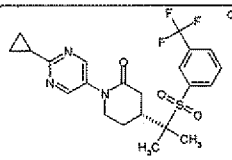
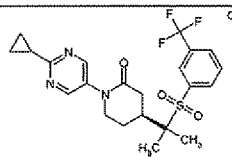
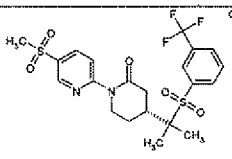
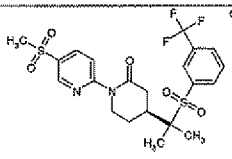
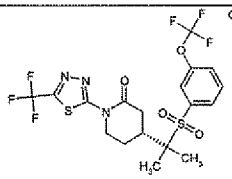
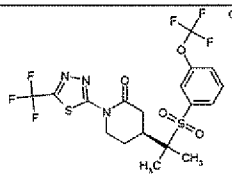
93		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495
94		*tert*-butyl 4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-2-oxopiperidine-1-carboxylate	466
95		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(1*H*-1,2,4-triazol-3-yl)piperidin-2-one	417
96		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]piperidin-2-one	502
97		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]piperidin-2-one	502
98		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-{(1*R*)-1-[3-(trifluoromethyl)phenyl]ethyl}piperidin-2-one	522
99		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-{(1*S*)-1-[3-(trifluoromethyl)phenyl]ethyl}piperidin-2-one	522

100		(4*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)piperidin-2-one	528
101		(4*S*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)piperidin-2-one	528
102		(4*R*)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)piperidin-2-one	529
103		(4*S*)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)piperidin-2-one	529
104		(4*R*)-4-(1-methyl-1-{[3-(methylsulfonyl)phenyl]sulfonyl}ethyl)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]piperidin-2-one	582
105		(4*S*)-4-(1-methyl-1-{[3-(methylsulfonyl)phenyl]sulfonyl}ethyl)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]piperidin-2-one	582
106		(4*R*)-4-(1-methyl-1-{[3-(methylsulfonyl)phenyl]sulfonyl}ethyl)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	583

107		(4*S*)-4-(1-methyl-1-{[3-(methylsulfonyl)phenyl]sulfonyl}ethyl)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	583
108		1-{4-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyridin-2(1*H*)-one	519
109		1-{4-[(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyridin-2(1*H*)-one	519
110		(4*R*)-1-[4-(methylsulfonyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	504
111		(4*S*)-1-[4-(methylsulfonyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	504
112		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(4-pyridin-4-ylphenyl)piperidin-2-one	503
113		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(4-pyridin-4-ylphenyl)piperidin-2-one	503
114		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(4-pyridin-2-ylphenyl)piperidin-2-one	503

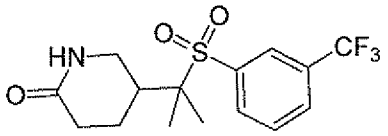
115		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(4-pyridin-2-ylphenyl)piperidin-2-one	503
116		(4*R*)-1-[4-(1*H*-imidazol-1-yl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	492
117		(4*S*)-1-[4-(1*H*-imidazol-1-yl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	492
118		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]piperidin-2-one	493
119		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]piperidin-2-one	493
120		3-{4-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyridinium trifluoroacetate	503
121		3-{4-[(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyridinium trifluoroacetate	503
122		5-{4-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyrimidin-1-ium trifluoroacetate	504

123		5-{4-[(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyrimidin-1-ium trifluoroacetate	504
124		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]piperidin-2-one	512
125		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]piperidin-2-one	512
126		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	511
127		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	511
128		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	511
129		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one	511

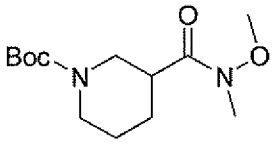
130		(4*R*)-1-(2-cyclopropylpyrimidin-5-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	468
131		(4*S*)-1-(2-cyclopropylpyrimidin-5-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	468
132		(4*R*)-1-[5-(methylsulfonyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	505
133		(4*S*)-1-[5-(methylsulfonyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	505
134		(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]piperidin-2-one	518
135		(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]piperidin-2-one	518

EXAMPLE 136

5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one



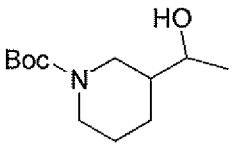
Step 1: *tert*-butyl 3-{[methoxy(methyl)amino]carbonyl}piperidine-1-carboxylate



To a stirred solution of 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid (50 g, 0.22 mol) in THF (600 mL) was added CDI (38.9 g, 0.24 mol) in portions at 0 °C. After the mixture was stirred at room temperature for 1 h, *N,O*-dimethylhydroxylamine hydrochloride (23.4 g, 0.24 mol) and TEA (28.7 g, 0.28 mol) were added in one portion. The resulting mixture was stirred at room temperature overnight, and the solution was washed with 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound (56.9 g, 95%).

^{1}HNMR ($CDCl_3$) δ: 4.0~4.2(m, 2H), 3.70(s, 3H), 3.15(s, 3H), 2.65~2.90(m, 3H), 1.85~1.92(m, 1H), 1.50~1.75(m, 3H), 1.39(s, 9H).

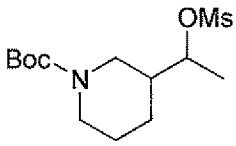
Step 2: *tert*-butyl 3-(1-hydroxyethyl)piperidine-1-carboxylate



To a flask was charged with *tert*-butyl 3-{[methoxy(methyl)amino]carbonyl}piperidine-1-carboxylate (50 g, 0.184 mol) and THF (250 mL), then methylmagneium bromide (74 mL, 0.22 mol) was added at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1h and was quenched by addition of sat. NH_4Cl (100 mL). The resulting mixture was extracted with ethyl acetate (200 mL×3), washed with water, dried over Na_2SO_4, filtered and concentrated to give the methyl ketone intermediate. This material was dissolved in MeOH (100 mL), and $NaBH_4$ (3.34 g, 0.09 mol) was added in portions at 0 °C. The reaction mixture was stirred at 0 °C for 30 minutes and was diluted with 10% KOH (20 mL). The organic solvent was removed in vacuum and extracted with EA (100 mL×3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give title compound (39 g, 96.7%).

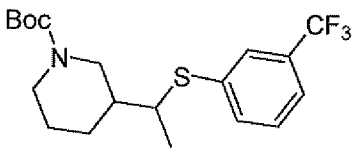
^{1}HNMR ($CDCl_3$) δ: 3.95~4.00(m, 1H), 3.60~3.70(m, 1H), 3.02~3.20(m, 1H), 2.60~2.80(m, 1H), 1.90~2.10(m, 2H), 1.60~1.80(m, 2H), 1.40~1.52(m, 1H), 1.25 (s, 3H).

Step 3: *tert*-butyl 3-{1-[(methylsulfonyl)oxy]ethyl}piperidine-1-carboxylate



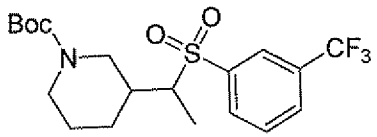
To a solution of *tert*-butyl 3-(1-hydroxyethyl)piperidine-1-carboxylate (20 g, 87 mmol) in DCM (100 mL) was added TEA (24.3 mL, 0.104 mol), and methanesulfonyl chloride (8.16 mL, 0.104 mol) at 0 °C. The resulting mixture was stirred for 30 minutes. Water (150 mL) was added and the mixture was extracted with DCM (150 mL×3). The combined organic layers were washed with 1N HCl (150 mL), sat. Na_2CO_3 (100 mL), and brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound as a light yellow sticky oil (36.3 g, 96%).
^{1}HNMR ($CDCl_3$) δ: 4.57~4.65(m, 1H), 4.10~4.20(m, 2H), 3.02(s, 3H), 2.60~2.70(m, 2H), 1.61~1.82(m, 3H), 1.45(s, 9H), 1.40(s, 3H), 1.20~1.30 (m, 2H).

Step 4: *tert*-butyl 3-(1-{[3-(trifluoromethyl)phenyl]thio}ethyl)piperidine-1-carboxylate



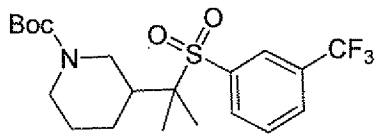
To a flask was added *tert*-butyl 3-{1-[(methylsulfonyl)oxy]ethyl}piperidine-1-carboxylate (24 g, 76.8 mmol), 3-trifluoromethyl-benzenethiol (16.5 g, 92.2 mmol), K_2CO_3 (32 g, 0.23 mol) and DMF (250 mL), and the reaction mixture was stirred at 50 ℃ overnight. Then water (200 mL) was added and the resulting mixture was extracted with EtOAc (100 mL×3). The combined organics were washed with water (100 mL), 5 % KOH (50 mL), brine (50 mL) and dried over Na_2SO_4, filtered and concentrated. Crude product was purified by silica gel chromatography to give the title compound (8.76 g, 29 %).
^{1}HNMR ($CDCl_3$) δ: 7.75(s, 1H), 7.65(d, *J*=8 Hz, 1H), 7.50~7.55(m, 2H), 4.60~4.70(m, 1H), 3.90~4.15 (m, 2H), 3.02(s, 3H), 2.60~2.80(m, 2H), 1.65~1.85(m, 3H), 1.48(s, 9H), 1.20~1.30(m, 2H).
MS (M+1): 390

Step 5: *tert*-butyl 3-(1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidine-1-carboxylate



To a solution of *tert*-butyl 3-(1-{[3-(trifluoromethyl)phenyl]thio}ethyl)piperidine-1-carboxylate (27 g, 0.07 mol) in MeOH (300 mL) was added a solution of Oxone™ in 300 mL of water (after pH was adjusted to 3 with addition on K_2CO_3 solution), and the mixture was stirred at room temperature for 2 hours. After TLC showed the reaction was completed, the mixture was extracted with EtOAc (100 mL×3). Organics were washed sequentially with water (150 mL) and brine (150 mL). It was dried over Na_2SO_4, filtered and concentrated. Residue was purified by silica gel chromatography to give the title compound (7.2 g, 24 %).
^{1}HNMR ($CDCl_3$) δ: 8.10~8.20(m, 2H), 7.95(d, *J*=8 Hz, 1H), 7.70~7.80(m, 1H), 4.20~4.40(m, 1H), 3.85~4.10(m, 2H), 3.00~3.10(m, 1H), 2.60~2.85(m, 3H), 2.10~2.30(m, 1H), 1.65~1.75(m, 2H), 1.45(s, 9H), 1.20~1.30(m, 3H).
MS (M+1): 422

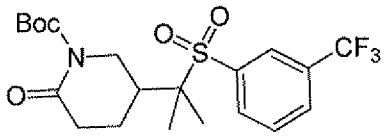
Step 6: *tert*-butyl 3-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidine-1-carboxylate



To a solution of *tert*-butyl 3-(1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidine-1-carboxylate (10.4 g, 24.7 mmol) in THF (150 mL) was added NaHMDS (18.5 mL, 37 mmol) at -78 °C under nitrogen atmosphere, and the mixture was stirred at -78 °C for 0.5 hour. Then MeI (3 mL, 49.4 mmol) was added dropwise. HPLC showed the reaction was completed, then the reaction was quenched with sat. NH_4Cl (100 mL) at -78 °C. The mixture was extracted with EtOAc (100 mL×3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound (9.9 g, 92 %).

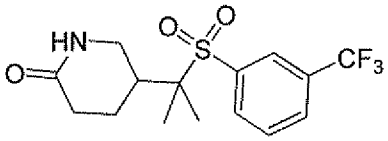
^{1}HNMR ($CDCl_3$) δ: 8.05~8.12(m, 2H), 7.85(d, *J*=8 Hz, 1H), 7.65(t, *J*=8 Hz, 1H), 3.95~4.10(m, 1H), 2.50~2.65(m, 2H), 2.00~2.28(m, 1H), 1.60~1.80(m, 3H), 1.46(s, 9H), 1.25 (s, 6H), 1.10~1.30(m, 2H).
MS (M+1): 436

Step 7: *tert*-butyl 5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidine-1-carboxylate



To a solution of *tert*-butyl 3-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidine-1-carboxylate (47.5 g, 0.11 mol) in CH_3CN / CCl_4 / H_2O (150 mL / 150 mL / 225 mL) were added $NaIO_4$ (94 g, 0.44 mol) and $RuCl_3$ (0.5 g, 2.4 mmol), and the resulting mixture was stirred at room temperature for two hours. TLC showed the starting material was consumed completely. It was extracted with EtOAc (200 mL×3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to give the title compound (20 g, 45 %).
^{1}HNMR ($CDCl_3$) δ: 8.12(s, 1H), 8.05(d, *J*=8 Hz, 1H), 7.85(d, *J*=8 Hz, 1H), 7.70(t, *J*=8 Hz, 1H), 4.10~4.15(m, 1H), 3.60~3.70(m, 1H), 2.50~2.60(m, 2H), 2.30~2.40(m, 2H), 2.05~2.10(m, 1H), 1.45(s, 9H), 1.30(s, 3H), 1.20(s, 3H).

Step 8: 5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one

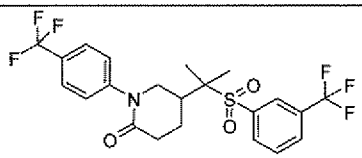
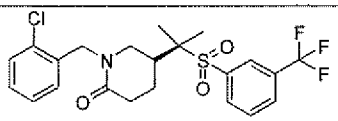
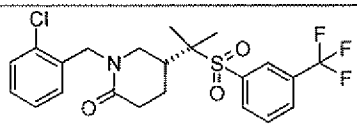
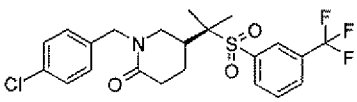
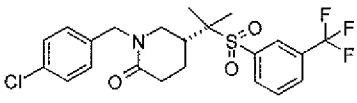


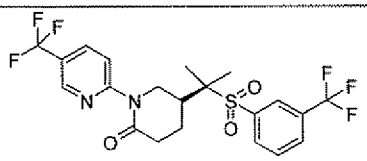
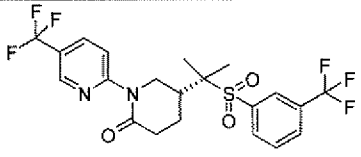
A solution of *tert*-butyl 5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidine-1-carboxylate (3 g, 6.8 mmol) in HCl/dioxane (4N, 60 mL) was stirred at room temperature for 1 hour. The organic solvent was removed in vacuum to give the title compound (2.5 g, 95 %).

^{1}HNMR (CD_3OD) δ: 8.16~8.20(m, 1H), 8.05~8.10(m, 2H), 7.85~7.95(m, 1H), 3.90~3.40(m, 1H), 3.45~3.55(m, 1H), 2.90~3.10(m, 2H), 2.40~2.50(m, 1H), 2.00~2.15(m, 2H), 1.65~1.85(m, 2H), 1.30(s, 3H), 1.20(s, 3H).

MS (M+1): 336

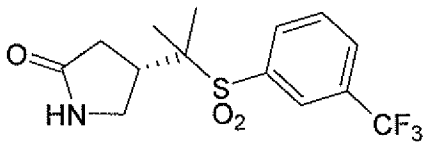
TABLE 2

EXAMPLE #	STRUCTURE	CHEMICAL NAME	MASS SPECTRAL DATA m/e (M+H)
137		5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]piperidin-2-one	494
138		(5S)-1-(2-chlorobenzyl)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	474
139		(5R)-1-(2-chlorobenzyl)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	474
140		(5S)-1-(4-chlorobenzyl)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	474
141		(5R)-1-(4-chlorobenzyl)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one	474

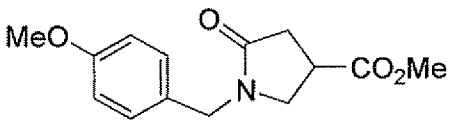
142		(5S)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl} ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495
143		(5R)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl} ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one	495

EXAMPLE 144

4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one



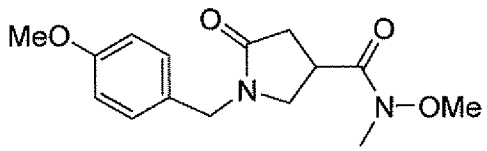
Step 1: methyl 1-(4-methoxybenzyl)-5-oxopyrrolidine-3-carboxylate



To a 250 ml round bottom flask were added 4-methoxybenzylamine (13 g, 95 mmol), dimethyl itaconate (10 g, 63.2 mmol), 10 ml water and 100 ml MeOH. The resulting reaction mixture was heated at 50 °C for 16 hours. Volatiles were removed. Residue was diluted with 150 ml EtOAc/ether (1:1), washed sequentially with 2x100 ml NH_4Cl (sat.), 100 ml brine. Organics were dried over sodium sulfate, filtered and concentrated to give 17 g pale yellow viscous material. It was used for next step of reaction without further purification.

^{1}H-NMR ($CDCl_3$): δ7.2 (d, J = 8.5 Hz, 2H), 6.9 (d, J = 8.4 Hz, 2H), 4.46 (d, J = 14.5 Hz, 1H), 4.40 (d, J = 14.4 Hz, 1H),3.83 (s, 3H), 3.74 (s, 3H), 3.5 (m, 2H) 3.2 (m, 1H), 2.8 (m, 2H).
Mass Spectra (m/e): 264 (M+1).

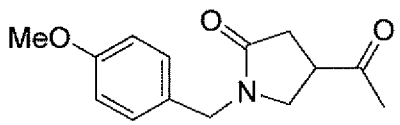
Step 2: *N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-5-oxopyrrolidine-3-carboxamide



To a 500 ml round bottom flask were added methyl 1-(4-methoxybenzyl)-5-oxopyrrolidine-3-carboxylate (17 g, 64.6 mmol), *N,O*-dimethylhydroxylamine hydrochloride (8.2g, 84 mmol) and 100 ml THF. The resulting mixture was stirred vigorously for 20 minutes until a fine suspension resulted. Isopropylmagnesium chloride in THF (81 ml, 2M, 161 mmol) was add via a syringe over 10 minutes at -10 °C. The resulting reaction mixture was stirred at this temperature for 30 more minutes. It was diluted with 150 ml ether, washed sequentially with 2x150 ml NH_4Cl (sat.), 100 ml brine. Organics were dried over sodium sulfate, filtered and concentrated. Residue was azeotropically dried by addition and pumping off toluene two times to give 13.5 g title compound as pale yellow solid. It was used for the next step of reaction without further purification.

^{1}H-NMR ($CDCl_3$): δ7.24 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.5 (d, J = 14.7 Hz, 1H), 4.35 (d, J = 14.6 Hz, 1H),3.82 (s, 3H), 3.70 (s, 3H), 3.5 (m, 3H) 3.21 (s, 3H), 2.85(m, 1H), 2.7 (m, 1H).
Mass Spectra (m/e): 293 (M+1).

Step 3: 4-acetyl-1-(4-methoxybenzyl)pyrrolidin-2-one

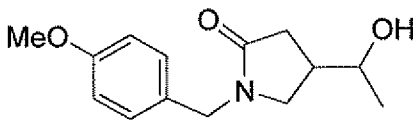


To a 250 ml round bottom flask were added *N*-methoxy-1-(4-methoxybenzyl)-*N*-methyl-5-oxopyrrolidine-3-carboxamide (13.5 g, 46.2 mmol) and 80 ml THF. The resulting mixture was cooled with dry ice acetone bath and methylmagnesium chloride THF solution (3M, 15.4 ml, 46.2 mmol). Significant amount of precipitation formed and stirring became difficult. Reaction mixture was allowed to warm up to room temperature and stirred for 10 more minutes. NMR indicated 90% conversion. The reaction mixture was cooled back to -78 °C. More THF (30 ml) and methylmagnesium chloride (3M, 1.4 ml, 4.2 mmol) was added. Reaction mixture was allowed to warm up room temperature. NMR indicated over 95% conversion. It was diluted with 150 ml ether, washed sequentially with 2x150 ml NH_4Cl (sat.),

100 ml brine. Organics were dried over sodium sulfate, filtered and concentrated. It was used for the next step of reaction without further purification.

^{1}H-NMR ($CDCl_3$): δ7.19 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.48 (d, J = 14.6 Hz, 1H), 4.36 (d, J = 14.6 Hz, 1H),3.8 (s, 3H), 3.5 (m, 1H), 3.39 (t, J = 9.3 Hz, 1H) 3.3 (m, 1H), 2.7(m, 2H), 2.2 (s, 3H).
Mass Spectra (m/e): 248 (M+1).

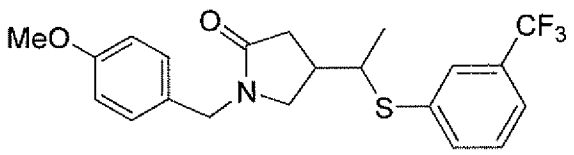
Step 4: 4-(1-hydroxyethyl)-1-(4-methoxybenzyl)pyrrolidin-2-one



To a 250 ml round bottom flask contains 4-acetyl-1-(4-methoxybenzyl)pyrrolidin-2-one (12.7 g, 51.5 mmol) and 100 ml MeOH was added sodium borohydride (0.97 g, 25.8 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 20 minutes. NMR indicated complete conversion. Volatiles were removed. Residue was partitioned between 150 ml 10% KOH and 150 ml EtOAc. Organics were washed with 100 ml brine, dried over sodium sulfate, filtered and concentrated to give title compound as sticky oil initially. It slowly crystallized on standing. This material was used for the next step of reaction without further purification.

^{1}H-NMR ($CDCl_3$): (mixture of distereomers) δ7.19 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.4 (m, 2H), 3.82 (s, 3H), 3.7 (m, 1H), 3.1-3.4 (m, 2H) 2.2-2.6 (m, 3H), 1.6 (br, 1H), 1.20 (d, J = 6.2 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H).
Mass Spectra (m/e): 250 (M+1).

Step 5: 1-(4-methoxybenzyl)-4-(1-{[3-(trifluoromethyl)phenyl]thio}ethyl)pyrrolidin-2-one

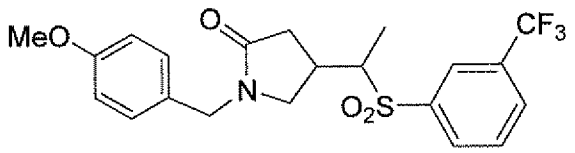


To a 250 ml round bottom flask contains 4-(1-hydroxyethyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (8.86 g, 40.4 mmol), TEA (16.9 ml, 121 mmol) and 100 ml dichloromethane was added MsCl (3.78 ml, 48.5 mmol) at 0 °C. The resulting mixture was

stirred at 0 °C for 30 minutes. NMR indicated complete conversion. Volatiles were removed. Residue was diluted with 300 ml EtOAc/ether (1:1). It was washed with 400 ml water, then 100 ml brine. Organics were dried over sodium sulfate, filtered and concentrated. Residue was dissloved in 100 ml DMF. 3-(Trifluoromethyl)benzenethiol (10.8 g, 60.6 mmol) was added, followed by potassium carbonate (12 g, 87 mmol). The resluting reaction mixture was heated at 60 °C for 16 hrs. It was diluted with 300 ml EtOAc, washed sequentially with 2x300 ml water, 100 ml brine. Organics were dried over sodium sulfate, filtered and concentrated to give 9 g title compound. It was used for the next step of reaction directly.

^{1}H-NMR ($CDCl_3$): (mixture of distereomers) δ 7.4-7.7 (m, 4H), 7.2 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.4 (m, 2H), 3.83 (s, 3H), 3.1-3.5 (m, 3H) 2.3-2.7 (m, 3H), 1.29 (d, J = 6.7 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H).
Mass Spectra (m/e): 410 (M+1).

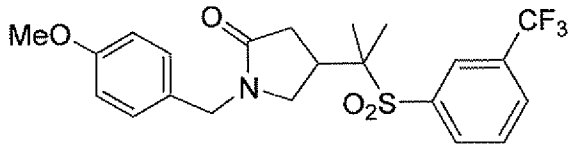
Step 6: 1-(4-methoxybenzyl)-4-(1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one



To a 1 L round bottom flask contains 1-(4-methoxybenzyl)-4-(1-{[3-(trifluoromethyl)phenyl]thio}ethyl)pyrrolidin-2-one (9 g, 22 mmol) and 300 ml MeOH was added Oxone™ (27 g, 44 mmol) dissolved in 200 ml water.The resulting mixture was stirred room temperature for 30 minutes. LC-Mass indicated complete conversion. The reaction mixture was diluted with 100 ml EtOAc, then filtered. Filtrate was concentrated. Residue was partitioned between 100 ml EtOAc and 100 ml brine. Organics were dried over sodium sulfate, filtered and concentrated. Residue was purified on silica gel column, eluted with 1:3 to 2:3 acetone/hexane to give 6.5 g title compound as viscous oil.

^{1}H-NMR ($CDCl_3$): (mixture of distereomers) δ 8.14 (s, 1H), 8.12 (s, 1H), 8.1 (m, 1H), 7.95 (m, 1H), 7.78 (m, 1H), 7.2 (m, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.4 (m, 2H), 3.84 (s, 3H), 2.4-3.6 (m, 6H), 1.19 (d, J = 6.7 Hz, 3H), 1.18 (d, J = 6.8 Hz, 3H).
Mass Spectra (m/e): 442 (M+1).

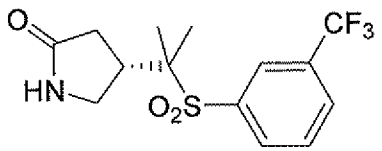
Step 7: 1-(4-methoxybenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one



To a 250 ml round bottom flask contains 1-(4-methoxybenzyl)-4-(1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one (7 g, 15.9 mmol) and 25 ml DMF was added potassium *tert*-butoxide (2.67 g, 23.8 mmol) dissolved in 15 ml DMF at – 65 °C, followed by iodomethane (1.98 ml, 31.7 mmol) immediately. The resulting mixture was allowed to warm up to room temperature and diluted with 150 ml EtOAc/ether (1:1). It was washed sequentially with 250 ml water, 2x50 ml brine. Organics were dried over sodium sulfate, filtered and concentrated. Residue was purified on silica gel column, eluted with 1:9 to 2:3 acetone/hexane to give 2.8 g title compound as viscous oil. The pair of enantiomers were separated on ChiralPak AD column eluted with 30% MeOH/CO_2 at 100 bar to give 1.25 g and 1.2 g each of the pure enantiomers with retention time of 3.6 min and 7.1 min (ChiralPak AD-H, 4.6x250mm, 15%MeOH/CO_2, 2.1 ml/min, 100 bar, 40 °C).

^{1}H-NMR ($CDCl_3$): δ: 8.11 (s, 1H), 8.05 (d, J = 7.7 Hz,1H), 7.98 (d, J = 8.1 Hz,1H),7.76 (t, J = 8.0 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.48 (d, J = 14.7 Hz, 1H), 4.36 (d, J = 14.6 Hz, 1H), 3.84 (s, 3H), 3.45 (m, 1H), 3.35 (m, 1H), 2.95 (m, 2H), 2.55 (m, 1H), 2.4 (m, 1H), 1.27 (s, 3H), 1.25 (s, 3H).
Mass Spectra (m/e): 456 (M+1).

Step 8: (4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one

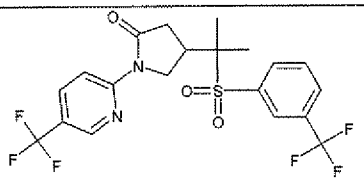
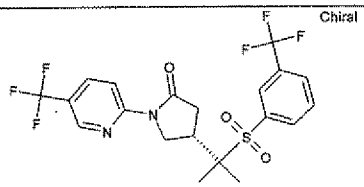


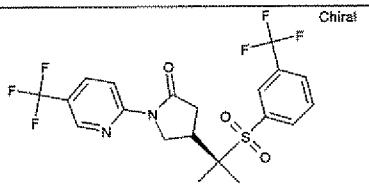
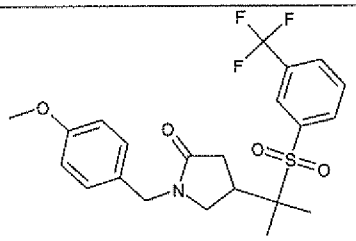
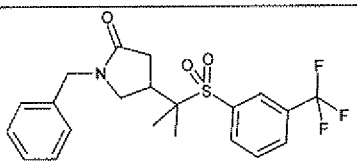
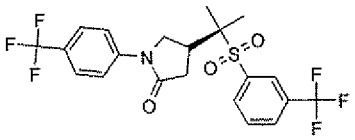
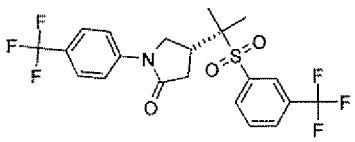
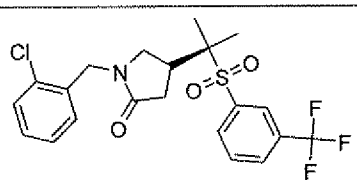
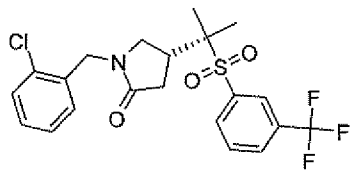
To a 250 ml round bottom flask were added (4*S*)-1-(4-methoxybenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one (1.25 g, 2.74 mmol), CAN (7.52 g, 13.7 mmol), 50 ml CH_3CN and 5 ml water. The resulting mixture was stirred at room

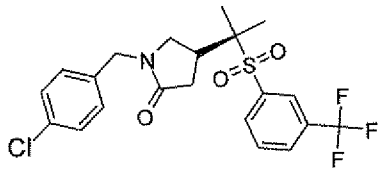
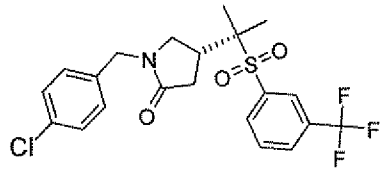
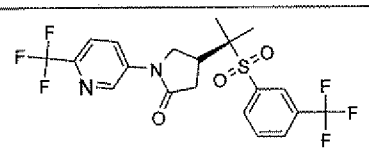
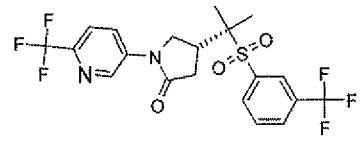
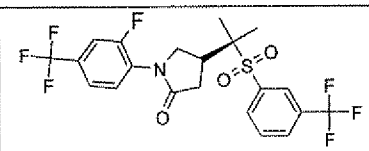
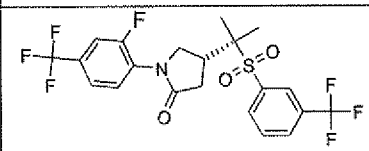
temperature overnight. Volatiles were removed. Residue was partitioned between 100 ml EtOAc and 100 ml water. Aqueous portion was extracted wtih 60 ml EtOAc. Organics were combined, washed with 30 ml brine, dried over sodium sulfate, filtered and concentrated. Residue was purified on silica gel column, washed initially with 1:1 EtOAc/hexane, then eluted with 1:10 CH_2Cl_2/MeOH to give 0.78 g title compound (absolute stereochemistry not determined) as pale yellow solid.

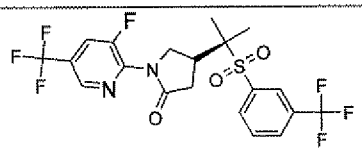
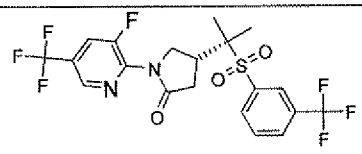
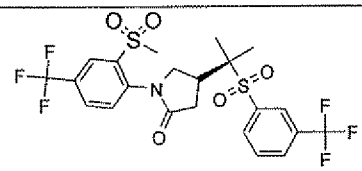
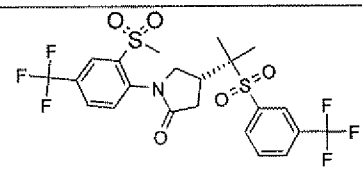
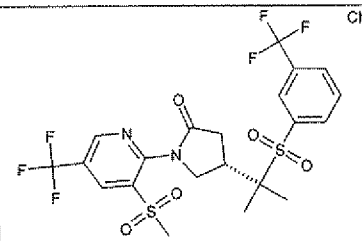
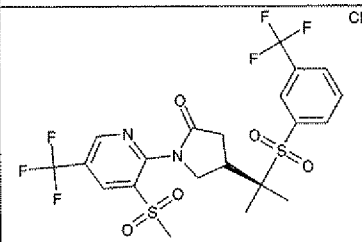
^{1}H-NMR ($CDCl_3$): δ; 8.17 (s, 1H), 8.11 (d, J = 8.0 Hz,1H), 8.0 (d, J = 7.8 Hz,1H),7.80 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 5.58 (br, 1H), 3.65 (m, 1H), 3.55 (m, 1H), 3.15 (m, 1H), 2.45 (m, 1H), 2.35 (m, 1H), 2.4 (m, 1H), 1.36 (s, 3H), 1.30 (s, 3H).
Mass Spectra (m/e): 336 (M+1).

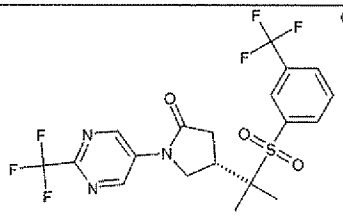
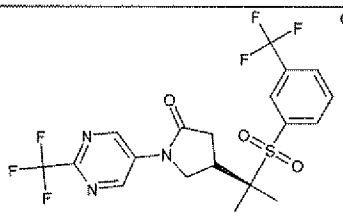
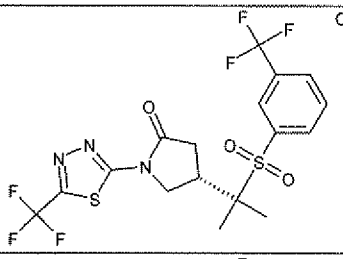
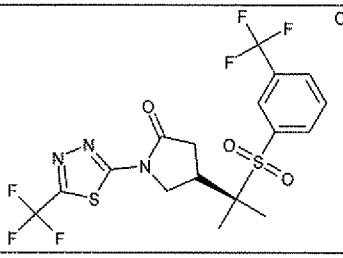
TABLE 3

EXAMPLE #	STRUCTURE	CHEMICAL NAME	MASS SPECTRAL DATA m/e (M+H)
146		4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidin-2-one	481
145		(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidin-2-one	481

146		(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidin-2-one	481
147		1-(4-methoxybenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	456
148		1-benzyl-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	426
149		(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-one	480
150		(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-one	480
151		(4S)-1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	460
152		(4R)-1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	460

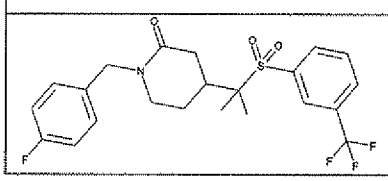
153		(4S)-1-(4-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	460
154		(4R)-1-(4-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	460
155		(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidin-2-one	481
156		(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidin-2-one	481
157		(4S)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	498
158		(4R)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	498

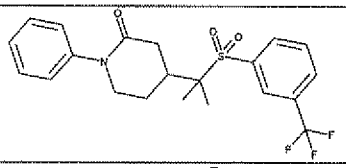
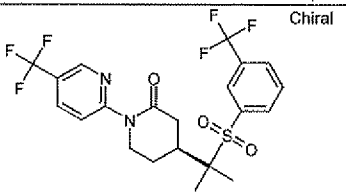
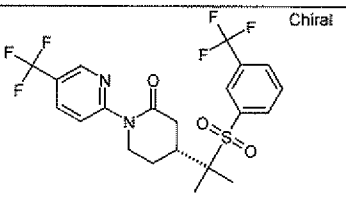
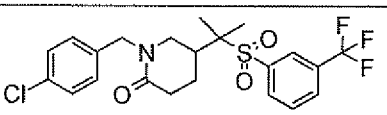
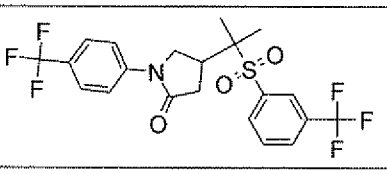
159		(4S)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	499
160		(4R)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	499
161		(4S)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	558
162		(4R)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	558
163		(4S)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	559
164		(4R)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one	559

165	 Chiral	(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]pyrrolidin-2-one	482
166	 Chiral	(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]pyrrolidin-2-one	482
167	 Chiral	(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]pyrrolidin-2-one	488
168	 Chiral	(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]pyrrolidin-2-one	488

The compounds described in this invention were evaluated for their biological activities using the assays described above. The data obtained for a representative set of compounds using Assay Example 1 is presentated in **TABLE 4**.

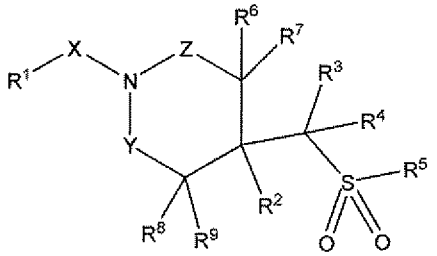
TABLE 4

STRUCTURE	**CaV2.2 IC_{50} (micromolar)**
	0.22

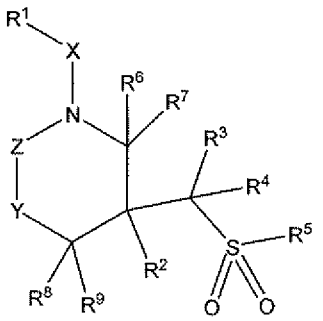
	0.36
 Chiral	0.64
 Chiral	0.28
	0.89
	0.79

WHAT IS CLAIMED IS:

1. A compound of structural formula I:



(I)



(II)

and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof:

X is a bond, $CR^{10}R^{11}$, C=O, C=ONR^{10}, CO_2, SO_2, C_{6-10} aryl, or C_{5-10} heteroaryl;
Y is $CR^{10}R^{11}$, C=O or absent;
Z is $CR^{10}R^{11}$, C=O or absent;
R^1 is H, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, OR^{10}, C(O) R^{10}, $(CH_2)_nC_{5-10}$ heterocycle, $(CH_2)_nC_{6-10}$ aryl, $(CH_2)_nC_{5-10}$ heteroaryl, fused aryl or fused heteroaryl, wherein said alkyl, cycloalkyl, heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a;
R^2 is H, C_{1-4} alkyl and C_{1-4}-perfluoroalkyl, C_{3-5}-cycloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, F, Cl, CN, $NR^{10}R^{11}$, wherein said alkyl, cycloalkyl, aryl and heteroaryl is optionally substituted with one to three groups of R^a;
R^3 and R^4 are each and independently selected from H, or C_{1-6} alkyl, C_{1-4}-perfluoroalkyl, C_{3-7}-cycloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, F, Cl, CN, OR^{10}, $NR^{10}R^{11}$, SO_2R^{10}, $SO_2NR^{10}R^{11}$, CO_2R^{10}, $CONHR^{10}$, $CONR^{10}R^{11}$, or R^3 and R^4 join to form a 3-7 member carbocyclic or

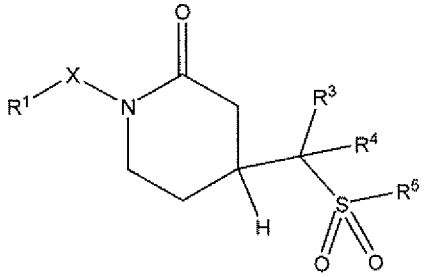
heterocyclic ring, wherein said alkyl, cycloalkyl, heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a;
R^5 is C_{6-10} aryl, C_{5-10} heteroaryl, C_{3-7} cycloalkyl, C_{5-10} heterocycle, wherein said cycloalkyl, heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a;
R^6, R^7, R^8, and R^9 independently represent H, C_{1-4}alkyl and C_{1-4}perfluoroalkyl, C_{3-6}-cycloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, F, Cl, CN, OR^{10}, $NR^{10}R^{11}$, or R^8 and R^9 combined with the carbon atom they are attached to can form C(O);
R^{10} and R^{11} are each and independently selected from H, or C_{1-6}alkyl, $(CH_2)_nC_{1-4}$-fluoroalkyl, C_{3-7}cycloalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, or R^{10} and R^{11} join to form a 3-7 member carbocyclic or heterocyclic ring with the atom to which they are attached; said alkyl, aryl, or heteroaryl optionally substituted with 1 to 3 groups of R^a,
n represents 0 to 6, and
R^a represents C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-4}-fluoroalkyl, C_{6-10} aryl, C_{5-10} heteroaryl, halogen, CN, $-OCF_3$, $-OCHF_2$, $-C(O)CF_3$, $-C(OR^{10})(CF_3)_2$, SR^{10}, $-OR^{10}$, $NR^{10}R^{11}$, SOR^{10}, SO_2R^{10}, $NR^{10}COR^{11}$, $NR^{10}COOR^{11}$, $NR^{10}CONR^{10}R^{11}$, $NR^{10}SO_2NR^{10}R^{11}$, $SO_2NR^{10}R^{11}$, $NR^{10}SO_2R^{11}$, CO_2R^{10}, $CONR^{10}R^{11}$, said aryl and heteroaryl optionally substituted with 1 to 3 groups of C_{1-6} alkyl, C_{3-7} cycloalkyl, halogen, CF_3, CN or OR^{10}; with the provisio that at least one of Y or Z is C=O.

2. The compound according to claim 1 wherein X is C=O, R^1 is $(CH_2)_nC_{5-10}$ heterocycle, $(CH_2)_nC_{6-10}$ aryl, $(CH_2)_nC_{5-10}$ heteroaryl, fused aryl or fused heteroaryl, and R^5 is C_{6-10} aryl, C_{5-10} heteroaryl, or C_{5-10} heterocycle, wherein said heterocycle, aryl and heteroaryl is optionally substituted with one to three groups of R^a.

3. The compound according to claim 2 wherein R^1 $(CH_2)_nC_{6-10}$ aryl.

4. The compound according to claim 2 wherein R^1 is $(CH_2)_nC_{5-10}$ $(CH_2)_nC_{5-10}$ heteroaryl.

5. The compound according to claim 1 represented by structural formulas Ia:

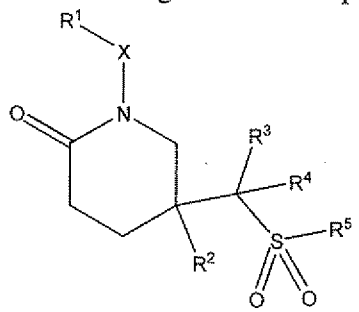


Ia

wherein X is C=O and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof

6. The compound according to claim 5 wherein both R^3 and R^4 are H or CH_3, or one of R^3 and R^4 is H and the other is CH_3, and R^1 and R^5 are independently phenyl, or pyridyl both optionally substituted with 1 to 3 groups of R^a.

7. The compound according to claim 1 represented by structural formulas IIa:

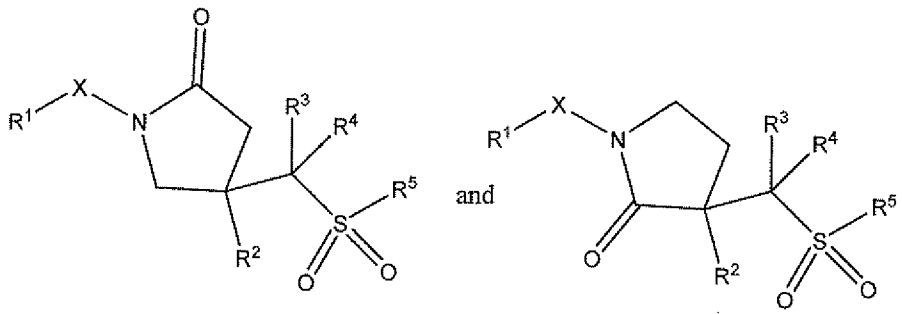


IIa

wherein X is C=O and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof

8. The compound according to claim 7 wherein both R^3 and R^4 are H or CH_3, or one of R^3 and R^4 is H and the other is CH_3, and R^1 and R^5 are independently phenyl, or pyridyl both optionally substituted with 1 to 3 groups of R^a.

9. The compound according to claim 1 represented by structural formula IIa or IIb:



IIa and IIb

wehrein X is C=O and R^2 is H, and pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

10. A compound which is:

(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
tert-butyl (4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidine-1-carboxylate;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]piperidin-2-one;
(4*R*)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-(2-bromobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-{[3-chloro-5-(trifluoromethyl)pyridin-2-yl]methyl}-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-benzoyl-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;

1-benzyl-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-(2-fluorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-(4-fluorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-(3-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-(4-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(1-phenylethyl)piperidin-2-one;
1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-(3-fluorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
1-[4-(methylsulfonyl)benzyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-phenylpiperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)phenyl]-piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)phenyl]-piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]-piperidin-2-one;
2-[4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)pyridinium trifluoroacetate;
1-[2-(methylsulfonyl)benzyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-piperidin-2-one;
1-[3-(methylsulfonyl)benzyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-

piperidin-2-one;
1-[5-fluoro-2-(methylsulfonyl)benzyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}-ethyl)piperidin-2-one;
1-[5-fluoro-2-(methylsulfonyl)benzoyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}-ethyl)piperidin-2-one;
1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)phenyl]-piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(2-naphthyl)piperidin-2-one;
2-[4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]quinolinium trifluoroacetate;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-{[5-(trifluoromethyl)pyridin-2-yl]methyl}piperidin-2-one;
1-isoquinolin-3-yl-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]piperidin-2-one;
(4*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-1-(1,3-benzothiazol-2-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-(1,3-benzothiazol-2-yl)-4-(1-methyl-1-{[3-

(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*R*)-1-[2-(methylthio)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[2-(methylthio)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethoxy)benzyl]-piperidin-2-one;
1-[1-(4-bromophenyl)cyclopropyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}-ethyl)piperidin-2-one;
1-[1-(4-bromophenyl)-1-methylethyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}-ethyl)piperidin-2-one;
1-(5-chloropyrimidin-2-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-quinoxalin-2-ylpiperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-quinoxalin-2-ylpiperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)quinoxalin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)quinoxalin-2-yl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one;

(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one;
methyl 2-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)benzoate;
2-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)benzoic acid;
N-methyl-2-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)benzamide;
N,*N*-dimethyl-2-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]-5-(trifluoromethyl)benzamide;
(4*S*)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridazin-3-yl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one;
(4*R*)-1-[4-chloro-5-(trifluoromethyl)pyrimidin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[4-chloro-5-(trifluoromethyl)pyrimidin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*S*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[7-(trifluoromethyl)quinolin-3-yl]piperidin-2-one;
(4*R*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*S*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-

(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyrazin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyrazin-2-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)phenyl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)phenyl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)phenyl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)phenyl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[3-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
tert-butyl 4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-2-oxopiperidine-1-

carboxylate;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(1*H*-1,2,4-triazol-3-yl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-{(1*R*)-1-[3-(trifluoromethyl)phenyl]ethyl}piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-{(1*S*)-1-[3-(trifluoromethyl)phenyl]ethyl}piperidin-2-one;
(4*R*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(methylsulfonyl)phenyl]sulfonyl}ethyl)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(methylsulfonyl)phenyl]sulfonyl}ethyl)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(methylsulfonyl)phenyl]sulfonyl}ethyl)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(methylsulfonyl)phenyl]sulfonyl}ethyl)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
1-{4-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyridin-2(1*H*)-one;
1-{4-[(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyridin-2(1*H*)-one
(4*R*)-1-[4-(methylsulfonyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}-ethyl)piperidin-2-one;
(4*S*)-1-[4-(methylsulfonyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]-sulfonyl}ethyl)piperidin-2-one;

(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(4-pyridin-4-ylphenyl)piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(4-pyridin-4-ylphenyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(4-pyridin-2-ylphenyl)piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-(4-pyridin-2-ylphenyl)piperidin-2-one;
(4*R*)-1-[4-(1*H*-imidazol-1-yl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}-ethyl)piperidin-2-one;
(4*S*)-1-[4-(1*H*-imidazol-1-yl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]-sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]piperidin-2-one;
3-{4-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyridinium trifluoroacetate;
3-{4-[(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyridinium trifluoroacetate;
5-{4-[(4*R*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyrimidin-1-ium trifluoroacetate;
5-{4-[(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-2-oxopiperidin-1-yl]phenyl}pyrimidin-1-ium trifluoroacetate;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-

3-yl]piperidin-2-one;
(4*R*)-1-(2-cyclopropylpyrimidin-5-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl-}ethyl)piperidin-2-one;
(4*S*)-1-(2-cyclopropylpyrimidin-5-yl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}-ethyl)piperidin-2-one;
(4*R*)-1-[5-(methylsulfonyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]-sulfonyl}ethyl)piperidin-2-one;
(4*S*)-1-[5-(methylsulfonyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]-sulfonyl}ethyl)piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]piperidin-2-one;

5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one

5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]piperidin-2-one;
(5S)-1-(2-chlorobenzyl)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(5R)-1-(2-chlorobenzyl)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(5S)-1-(4-chlorobenzyl)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(5R)-1-(4-chlorobenzyl)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)piperidin-2-one;
(5S)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(5R)-5-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidin-2-one;
(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]pyrrolidin-2-one;
(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-

yl]pyrrolidin-2-one;
1-(4-methoxybenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
1-benzyl-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]pyrrolidin-2-one;
(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)phenyl]-pyrrolidin-2-one;
(4S)-1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4R)-1-(2-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4S)-1-(4-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4R)-1-(4-chlorobenzyl)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidin-2-one;
(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]pyrrolidin-2-one;
(4S)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]-sulfonyl}ethyl)pyrrolidin-2-one;
(4R)-1-[2-fluoro-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]-sulfonyl}ethyl)pyrrolidin-2-one;
(4S)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-

(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4R)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4S)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4R)-1-[2-(methylsulfonyl)-4-(trifluoromethyl)phenyl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4S)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4R)-1-[3-(methylsulfonyl)-5-(trifluoromethyl)pyridin-2-yl]-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)pyrrolidin-2-one;
(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]pyrrolidin-2-one;
(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]pyrrolidin-2-one;
(4S)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]pyrrolidin-2-one;
(4R)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl]pyrrolidin-2-one;

or pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

11. The compound according to claim 8 which is:

(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[2-(trifluoromethyl)pyrimidin-5-yl]piperidin-2-one;
(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;

(4*R*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethoxy)phenyl]sulfonyl}ethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*R*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*S*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[5-(trifluoromethyl)pyridin-2-yl]piperidin-2-one;
(4*R*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*S*)-4-(1-{[3-fluoro-5-(trifluoromethyl)phenyl]sulfonyl}-1-methylethyl)-1-[6-(trifluoromethyl)pyridin-3-yl]piperidin-2-one;
(4*S*)-4-(1-methyl-1-{[3-(trifluoromethyl)phenyl]sulfonyl}ethyl)-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidin-2-one;

or pharmaceutically acceptable salts thereof and individual enantiomers and diastereomers thereof.

12. A pharmaceutical composition comprising an inert carrier and an effective amount of a compound according to Claim 1.

13. A method for treating or preventing chronic or acute pain in a mammalian patient in need thereof comprising administering to said patient a therapeutically effective amount, or a prophylactically effective amount, of a compound of claim 1, or a pharmaceutically acceptable salt thereof.

14. A method for treating or preventing chronic or acute pain in a mammalian patient in need thereof comprising administering to said patient a therapeutically effective amount, or a prophylactically effective amount, of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.

15. A method for treating or controlling epilepsy in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1, or a pharmaceutically acceptable salt thereof.

16. A method for enhancing the quality of sleep in a mammalian patient in need thereof which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 09/57617

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 315/00 (2009.01)
USPC - 568/33
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC (8): C07C 315/00 (2009.01)
USPC: 568/33

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC (8): C07C 315/00 (2009.01) (See keywords below)
USPC: 568/33 ; 568/34 ; 568/35 ;560/17 ; 562/30; 562/37 ; 564/84 ; 564/86 (See keywords below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST: DB=PGPB,USPT,USOC,EPAB,JPAB : Google: Scholar/Patents: aryl sulfone calcium channel blockers pain sleep epilepsy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2007/075524 A2 (CHAKRAVARTY et al) 05 July 2007 (05.07.2007) pg 2 to pg 5; pg 8 to 12,	1-16
Y	US 2006/0111347 A1 (ASKEW et al) 25 May 2006 (25.05.2006) para [0014]; [0015];[0023];[0029];[0030]	1-16

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2009 (14.11.2009)	25 NOV 2009
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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