SUBSTITUTED 5-HETEROARYL-1-PHENYL-PYRAZOLE CANNABINOID MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

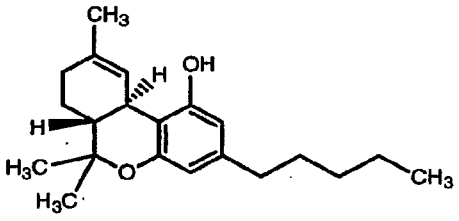
This present application claims benefit of U.S. Provisional Patent Application Serial No.60/739,129, filed November 23, 2005, which is incorporated herein by reference in its entirety and for all purposes.

FIELD OF THE INVENTION

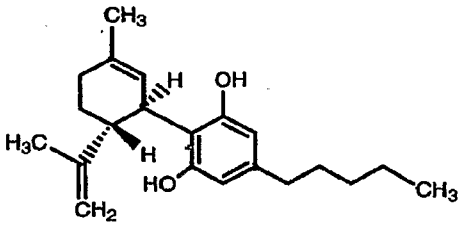
This invention is directed to substituted 5-heteroaryl-1-phenyl-pyrazole cannabinoid (CB) modulator compounds and methods for use in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease.

BACKGROUND OF THE INVENTION

Before the discovery of the cannabinoid CB1 and CB2 receptors, the term cannabinoid was used to describe the biologically active components of *cannabis sativa*, the most abundant of which are delta-9-tetrahydrocannabinol (THC) and cannabidiol.



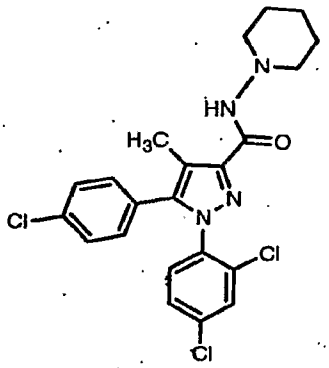
THC



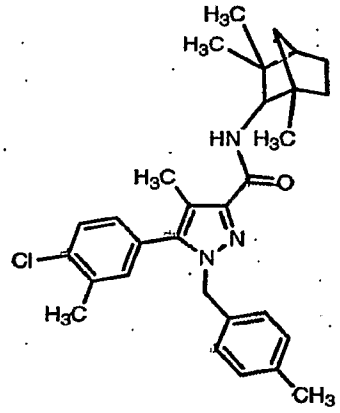
CANNABIDIOL

THC is a moderately potent partial agonist of the CB1 and CB2 receptors and is considered the "classical cannabinoid," a term now used to refer to other analogues and derivatives that are structurally related to the tricyclic dibenzopyran THC core. The term "nonclassical cannabinoid" refers to cannabinoid agonists structurally related to cannabidiol.

Pharmacological investigations have concentrated on selective CB receptor modulators of the pyrazole structural class, which include SR 141716A (the monohydrochloride salt of SR 141716) and SR 144528.



SR 141716



SR 144528

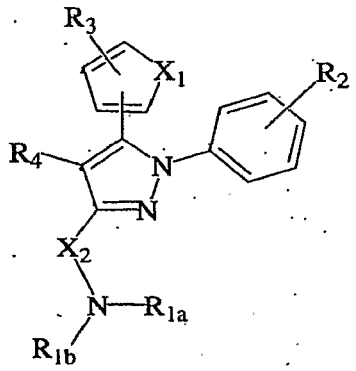
Pyrazole cannabinoid modulators are one among the many different structural classes which have aided the development of CB pharmacology, have helped to determine the biological effects mediated by the cannabinoid receptors, will lead to further refinement of current compounds and will be a source of new chemical classes in the future.

Certain compounds (including SR 141716, SR 144528 and the like) that were originally classified as selective antagonists are now considered to act as "inverse agonists" rather than pure antagonists. Inverse agonists have the ability to decrease the constitutive level of receptor activation in the absence of an agonist instead of only blocking the activation induced by agonist binding at the receptor. The constitutive activity of CB receptors has important implications since there is a level of continuous signaling by both CB1 and CB2 even in the absence of an agonist. For example, SR 141716A increases CB1 protein levels and sensitizes cells toward agonist action, thus indicating that inverse agonists may be another class of ligands used to modulate the endocannabinoid system and the downstream signaling pathways activated by CB receptors.

Advances in the synthesis of CB and cannabimimetic ligands have furthered the development of receptor pharmacology and provided evidence for the existence of additional cannabinoid receptor sub-types. However, there remains an ongoing need for the identification and development of CB1 or CB2 receptor cannabinoid modulators for the treatment of a variety of CB receptor modulated syndromes, disorders and diseases.

SUMMARY OF THE INVENTION

The present invention is directed to a compound of formula (I):



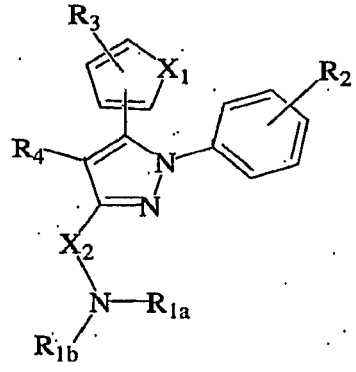
or a form thereof, useful as a cannabinoid receptor modulator, wherein R_{1a}, R_{1b}, X_1, X_2, R_2, R_3 and R_4 are as defined herein.

The present invention is also directed to a method for use of a compound of formula (I) in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease.

The present invention is further directed to a method for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a patient in need thereof comprising administering to the patient an effective amount of a compound of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to a compound having a structure according to formula (I):



or a form thereof, wherein

X_1 is N, O or S;

X_2 is carbonyl, alkenyl-carbonyl or alkenyl-sulfonyl;

R_{1a} is absent or hydrogen,

wherein R_{1a} is absent when R_{1a} and R_{1b} are taken together with the formula (I) nitrogen atom to form a heterocyclyl ring optionally substituted with one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, oxo, amino or aminoalkyl,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl;

R_{1b} is selected from C_{3-12} cycloalkyl, heterocyclyl, aryl, heteroaryl or alkyl substituted with C_{3-12} cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein each of C_{3-12} cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, oxo, amino or aminoalkyl,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl, and

wherein heterocyclyl optionally has one nitrogen ring atom and said atom is attached to the formula (I) nitrogen atom, and wherein said atom is optionally further substituted with alkyl to form a quaternary ammonium salt;

R_2 is one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, amino, aminoalkyl, aminosulfonylalkyl or sulfonylaminoalkyl,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl;

R_3 is one or two substituents selected from hydrogen, alkyl, alkoxy, cyano or halogen,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl; and,

R_4 is one, two or three substituents selected from alkyl, alkoxy, cyano or halogen, wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl.

An example of the present invention is a compound of formula (I) or a form thereof, wherein X_1 is O or S.

An example of the present invention is a compound of formula (I) or a form thereof, wherein X_2 is carbonyl or alkenyl-sulfonyl.

An example of the present invention is a compound of formula (I) or a form thereof, wherein R_{1a} is hydrogen.

An example of the present invention is a compound of formula (I) or a form thereof, wherein R_{1a} is absent when R_{1a} and R_{1b} are taken together with the formula (I) nitrogen atom to form a heterocyclyl ring optionally substituted with one or two substituents selected from alkyl, hydroxy or oxo.

An example of the present invention is a compound of formula (I) or a form thereof, wherein

R_{1b} is selected from heterocyclyl or alkyl substituted with C_{3-12} cycloalkyl, aryl or heteroaryl; wherein each of C_{3-12} cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, oxo, amino or aminoalkyl,

wherein heterocyclyl optionally has one nitrogen ring atom and said atom is attached to the formula (I) nitrogen atom, and wherein said atom is optionally further substituted with alkyl to form a quaternary ammonium salt.

An example of the present invention is a compound of formula (I) or a form thereof, wherein R_2 is one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, amino, aminoalkyl, aminosulfonylalkyl or sulfonylaminoalkyl.

An example of the present invention is a compound of formula (I) or a form thereof, wherein R_2 is one, two, three or four halogen substituents.

An example of the present invention is a compound of formula (I) or a form thereof, wherein R_3 is one or two substituents selected from hydrogen, alkyl, alkoxy, cyano or halogen.

An example of the present invention is a compound of formula (I) or a form thereof, wherein R_3 is one or two substituents selected from hydrogen, alkyl or halogen.

An example of the present invention is a compound of formula (I) or a form thereof, wherein R_4 is one, two or three substituents selected from alkyl, alkoxy, cyano or halogen.

An example of the present invention is a compound of formula (I) or a form thereof, wherein R_4 is one, two or three substituents selected from alkyl or cyano.

An example of the present invention is a compound of formula (I) or a form thereof, wherein

X_1 is O or S;

X_2 is carbonyl or alkenyl-sulfonyl;

R_{1a} is absent or hydrogen,

wherein R_{1a} is absent when R_{1a} and R_{1b} are taken together with the formula (I) nitrogen atom to form a heterocyclyl ring optionally substituted with one or two substituents selected from alkyl, hydroxy or oxo;

R_{1b} is selected from heterocyclyl or alkyl substituted with C_{3-12} cycloalkyl, aryl or heteroaryl, wherein each of C_{3-12} cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, oxo, amino or aminoalkyl,

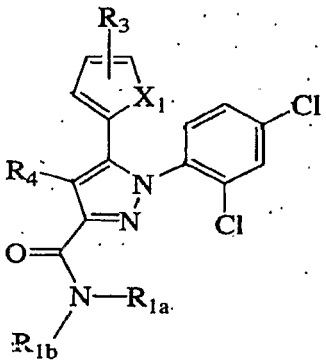
wherein heterocyclyl optionally has one nitrogen ring atom and said atom is attached to the formula (I) nitrogen atom, and wherein said atom is optionally further substituted with alkyl to form a quaternary ammonium salt;

R_2 is one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, amino, aminoalkyl, aminosulfonylalkyl or sulfonylaminoalkyl;

R_3 is one or two substituents selected from hydrogen, alkyl, alkoxy, cyano or halogen; and,

R_4 is one, two or three substituents selected from alkyl, alkoxy, cyano or halogen.

An example of the present invention is a compound of formula (Ia):



or a form thereof, wherein

X_1 is O or S;

R_{1a} is absent or hydrogen,

wherein R_{1a} is absent when R_{1a} and R_{1b} are taken together with the formula (I) nitrogen atom to form a heterocyclyl ring optionally substituted with one or two substituents selected from alkyl, hydroxy or oxo;

R_{1b} is selected from heterocyclyl or alkyl substituted with C_{3-12} cycloalkyl, aryl or heteroaryl, wherein heterocyclyl is optionally substituted with one substituent selected from alkyl, hydroxy or oxo,

wherein heterocyclyl optionally has one nitrogen ring atom and said atom is attached to the formula (I) nitrogen atom, and wherein said atom is optionally further substituted with alkyl to form a quaternary ammonium salt;

R_3 is one substituent selected from hydrogen, alkyl or halogen; and,

R_4 is one substituent selected from alkyl or cyano.

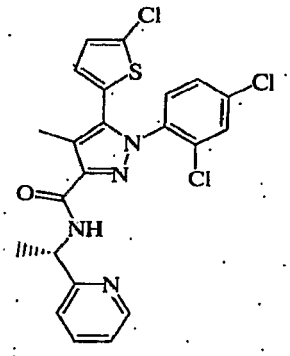
An example of the present invention is a compound of formula (Ia) or a form thereof wherein R_{1a}, R_{1b}, X_1, R_3 and R_4 are dependently selected from:

Cpd	R_{1a}	R_{1b}	X_1	R_3	R_4
1	H	(1*S*)-1-pyridin-2-yl-ethyl	S	5-Cl	CH_3

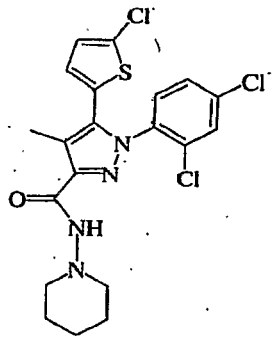
Cpd	R_{1a}	R_{1b}	X_1	R_3	R_4
2	H	piperidin-1-yl	S	5-Cl	CH_3
3	H	(1*S*)-1-phenyl-ethyl	S	5-Cl	CH_3
4	H	4-OH-piperidin-1-yl	S	5-Cl	CH_3
5	H	(1*R*)-1-cyclohexyl-ethyl	S	H	CH_3
6	H	(1*R*)-1-phenyl-ethyl	S	H	CH_3
7	H	(1*S*)-1-phenyl-ethyl	S	H	CH_3
8	H	(1*S*)-1-cyclohexyl-ethyl	S	H	CH_3
9	H	(1*S*)-1-pyridin-2-yl-ethyl	S	H	CH_3
10	H	piperidin-1-yl	S	H	CH_3
11	H	hexahydro-cyclopenta[c]pyrrol-2-yl	S	H	CH_3
12	H	(1*S*)-1-cyclohexyl-ethyl	S	5-Cl	CH_3
13	H	(1*R*)-1-cyclohexyl-ethyl	S	5-Cl	CH_3
14	H	(1*R*)-1-phenyl-ethyl	S	5-Cl	CH_3
15	H	piperidin-1-yl	S	5-Cl	CH_2CH_3
16	H	(1*R*)-1-phenyl-ethyl	S	H	CN
17	H	(1*R*)-1-pyridin-2-yl-ethyl	S	H	CN
18	H	(1*R*)-1-cyclohexyl-ethyl	S	H	CN
19	H	(1*S*)-1-phenyl-ethyl	S	H	CN
20	H	piperidin-1-yl	S	H	CN
21	---	piperidin-1-yl	S	H	CN
22	H	piperidin-1-yl	S	5-Br	CH_3
23	H	piperidin-1-yl	S	5-Cl	CN
24	H	(1*R*)-1-cyclohexyl-ethyl	S	5-Cl	CN
25	H	(1*R*)-1-phenyl-ethyl	S	5-Cl	CN
26	H	(1*S*)-1-phenyl-ethyl	S	5-Cl	CN
27	H	(1*R*)-1-pyridin-2-yl-ethyl	S	5-Cl	CN
28	H	piperidin-1-yl	S	5-F	CH_3
29	H	piperidin-1-yl	S	5-I	CH_3
30	H	2-oxo-piperidin-1-yl	S	5-Cl	CH_3
31	H	(1*S*)-1-phenyl-ethyl	S	5-F	CH_3
32	H	(1*R*)-1-phenyl-ethyl	S	5-F	CH_3
33	H	(1*S*)-1-cyclohexyl-ethyl	S	5-F	CH_3
34	H	(1*S*)-1-pyridin-2-yl-ethyl	S	5-F	CH_3
35	H	piperidin-1-yl	S	5-Br	CH_2CH_3
36	H	(1*S*)-1-phenyl-ethyl	S	5-I	CH_3
37	H	(1*S*)-1-pyridin-2-yl-ethyl	S	5-I	CH_3
38	H	(1*R*)-1-phenyl-ethyl	S	5-I	CH_3
39	H	(1*S*)-1-cyclohexyl-ethyl	S	5-I	CH_3
40	H	(1*R*)-1-phenyl-ethyl	S	5-Br	CH_2CH_3
41	H	(1*S*)-1-pyridin-2-yl-ethyl	S	5-Br	CH_2CH_3

Cpd	R_{1a}	R_{1b}	X_1	R_3	R_4
42	H	(1*S*)-1-phenyl-ethyl	S	5-Br	CH_2CH_3
43	H	(1*S*)-1-cyclohexyl-ethyl	S	5-Br	CH_2CH_3
44	H	piperidin-1-yl	S	4-Br	CH_3
45	---	piperidin-1-yl	S	4-Br	CH_3
46	H	(1*S*)-1-phenyl-ethyl	S	4-Br	CH_3
47	H	(1*S*)-1-pyridin-2-yl-ethyl	S	4-Br	CH_3
48	H	(1*S*)-1-cyclohexyl-ethyl	S	4-Br	CH_3
49	H	(1*R*)-1-phenyl-ethyl	S	4-Br	CH_3
50	---	4-OH-piperidin-1-yl	S	5-Br	CH_2CH_3
51	H	4-OH-piperidin-1-yl	S	5-Br	CH_2CH_3
52	H	1-CH_3-piperidin-1-yl	S	5-Br	CH_2CH_3
53	H	piperidin-1-yl	O	5-CH_3	CH_3
54	H	(1*S*)-1-phenyl-ethyl	O	5-CH_3	CH_3
55	H	(1*R*)-1-phenyl-ethyl	O	5-CH_3	CH_3
56	H	(1*R*)-1-pyridin-2-yl-ethyl	O	5-CH_3	CH_3
57	H	(1*R*)-1-cyclohexyl-ethyl	O	5-CH_3	CH_3

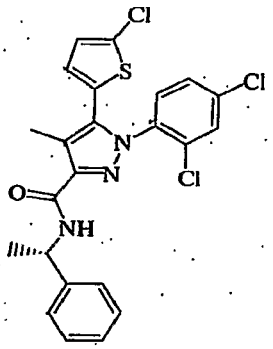
An example of the present invention is a compound or a form thereof selected from the group consisting of



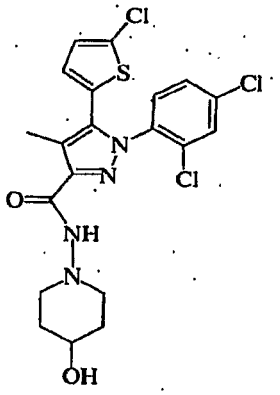
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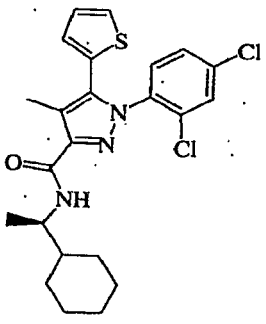
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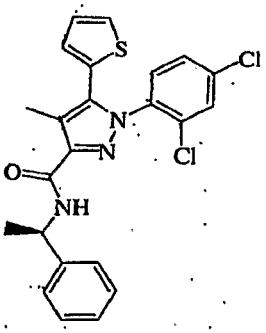
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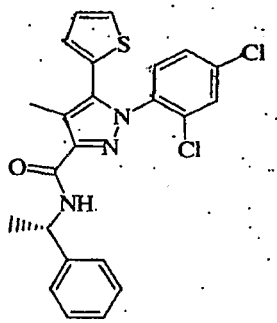
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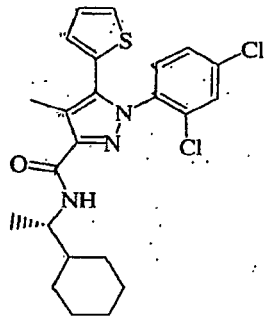
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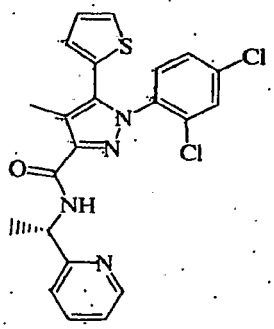
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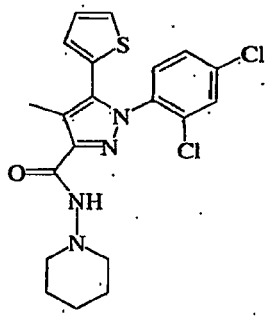
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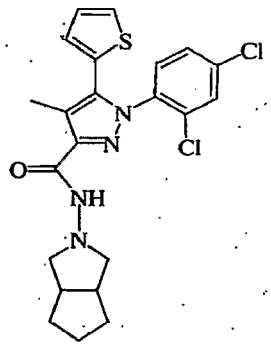
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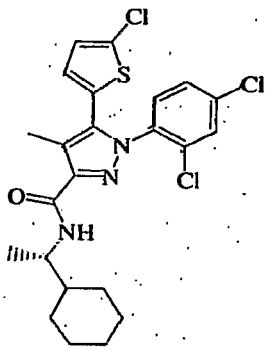
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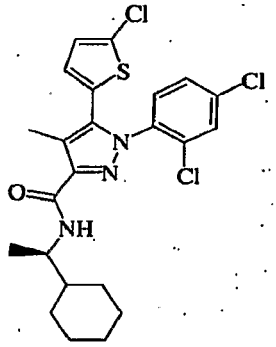
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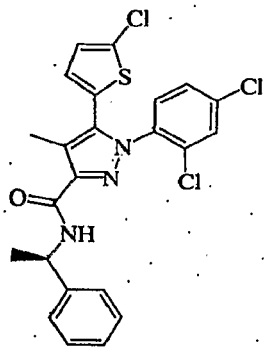
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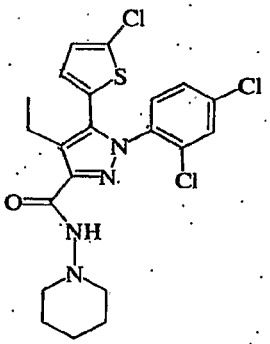
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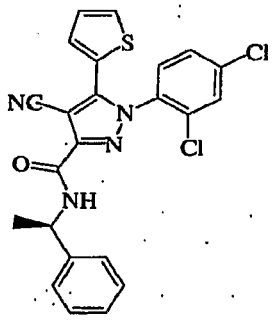
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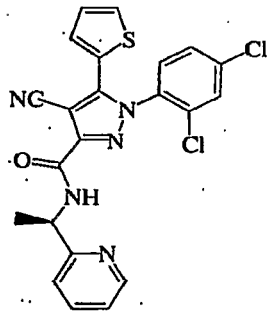
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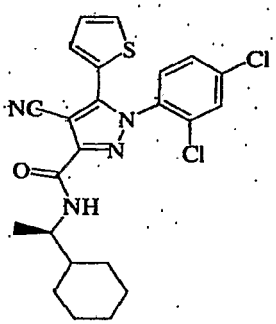
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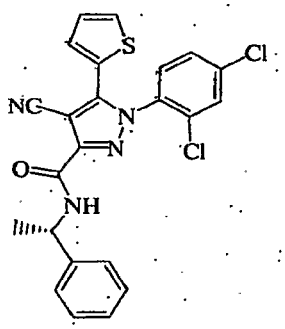
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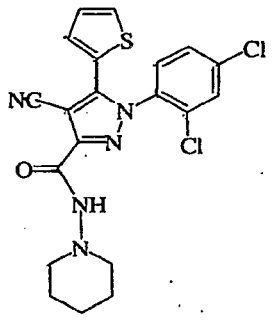
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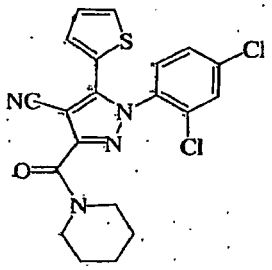
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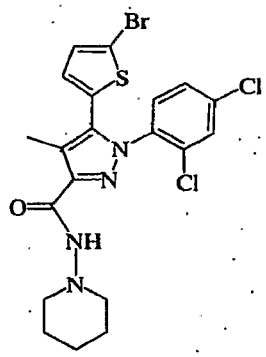
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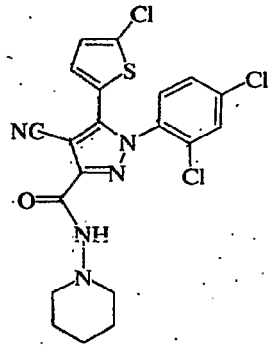
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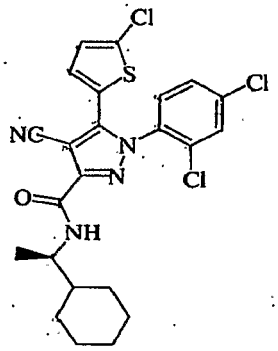
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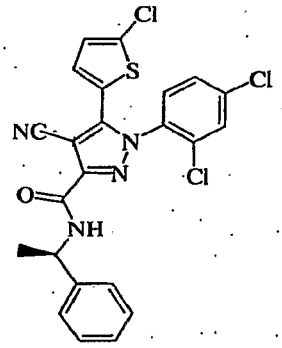
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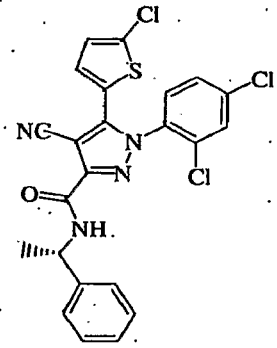
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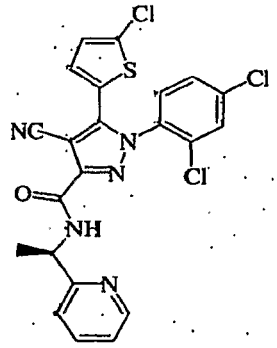
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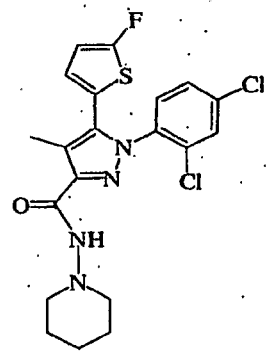
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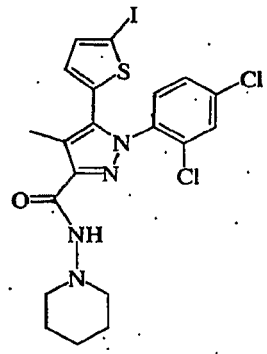
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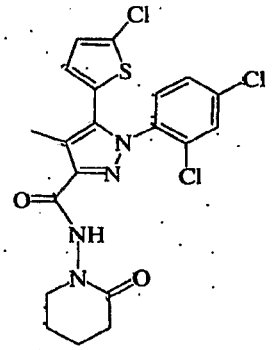
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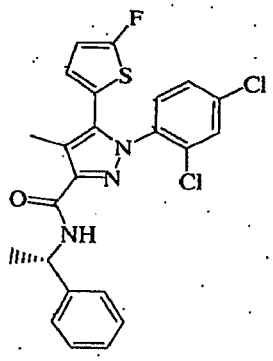
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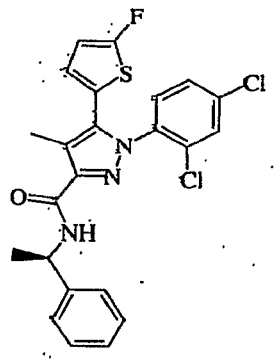
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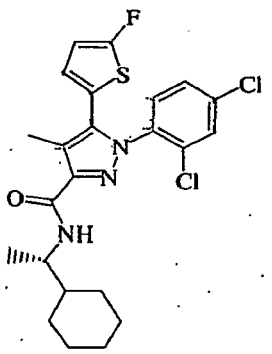
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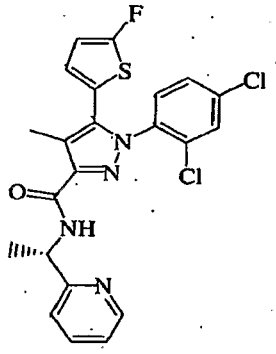
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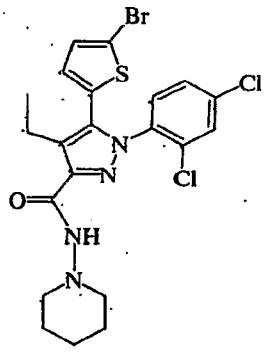
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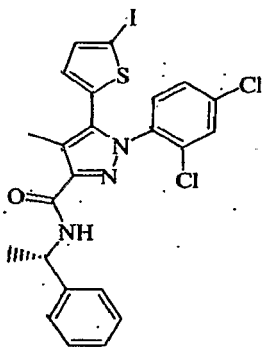
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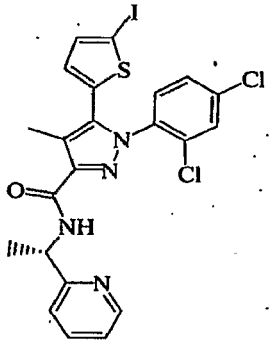
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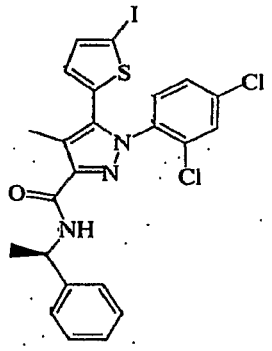
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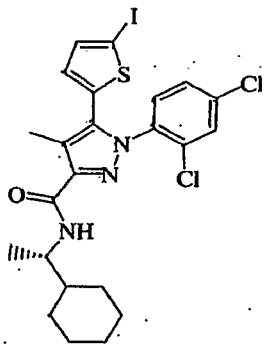
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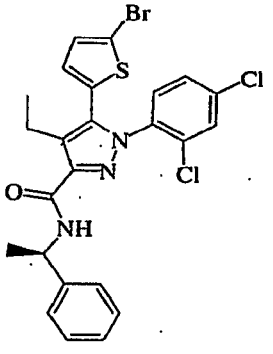
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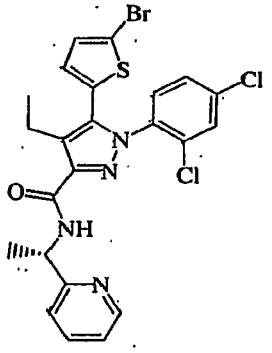
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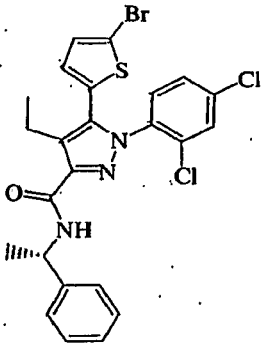
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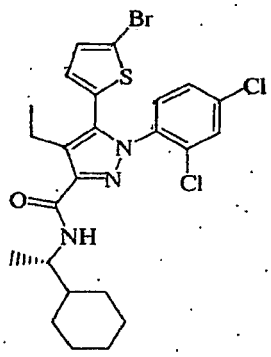
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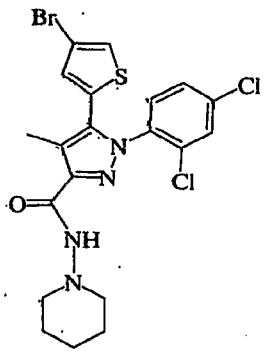
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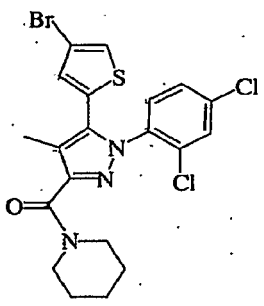
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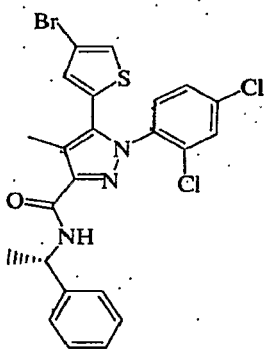
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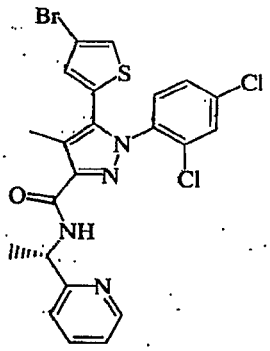
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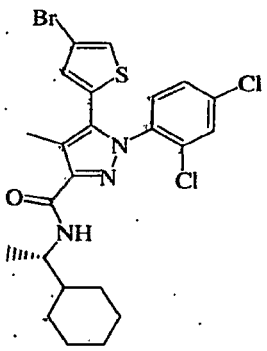
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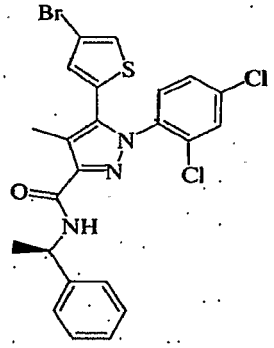
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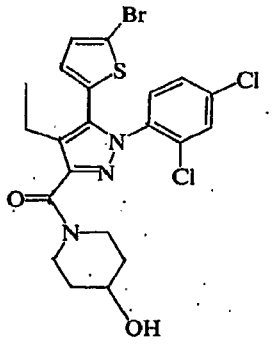
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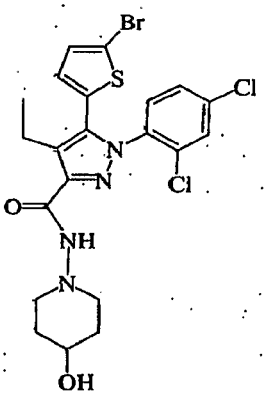
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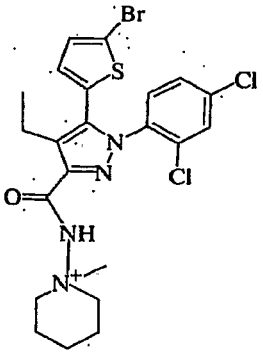
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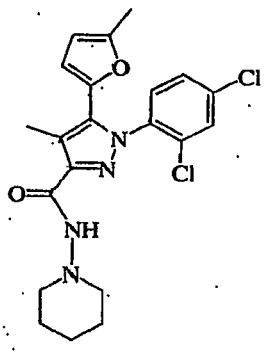
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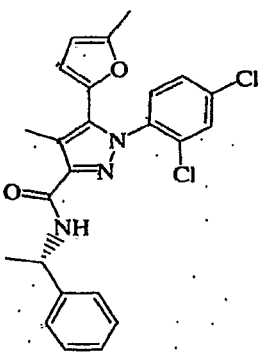
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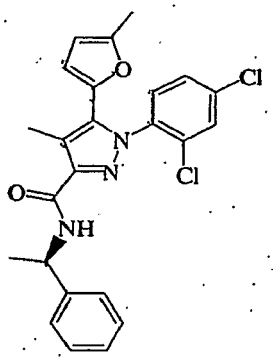
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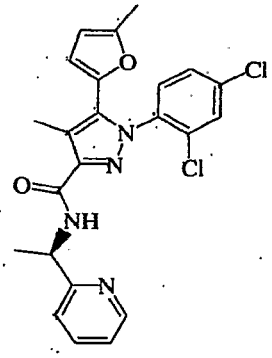
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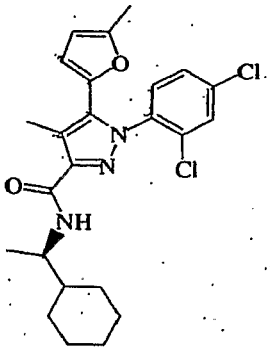
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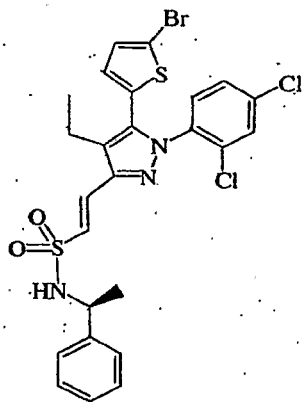
Cpd 55



Cpd 56



Cpd 57



Cpd 58

Definitions

As used herein, the following terms are intended to have the following definitions. The definitions herein may specify that the chemical term has an indicated formula. The particular formula provided is not intended to limit the scope of the invention, but is provided as an illustration of the term. The scope of the *per se* definition of the term is intended to include the plurality of variations expected to be included by one of ordinary skill in the art.

The term "alkyl" means a saturated branched or straight chain monovalent hydrocarbon radical of up to 10 carbon atoms. Alkyl typically includes, but is not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, pentyl, hexyl, heptyl and the like. When further substituted, substituent variables may be placed on any alkyl carbon atom.

The term "alkenyl" means a partially unsaturated branched or straight chain monovalent hydrocarbon radical of up to 10 carbon atoms having at least one carbon–carbon double bond, whereby the double bond is derived by the removal of one hydrogen atom from each of two adjacent carbon atoms. Atoms may be oriented about

the double bond in either the *cis* (Z) or *trans* (E) conformation. Alkenyl typically includes, but is not limited to, ethenyl (vinyl), propenyl (allyl or 2-propenyl), butenyl and the like. When further substituted, substituent variables may be placed on any alkyl carbon atom.

The term "alkoxy" means a radical of the formula: -O-alkyl. Alkoxy typically includes, but is not limited to, methoxy, ethoxy, propoxy, butoxy and the like. When further substituted, substituent variables may be placed on any alkoxy carbon atom.

The term "C_{3-12} cycloalkyl" means a saturated or partially unsaturated hydrocarbon ring system radical or linking group. The term "C_{3-12} cycloalkyl" also includes a C_{3-8} cycloalkyl, C_{3-10} cycloalkyl, C_{5-8} cycloalkyl, C_{5-12} cycloalkyl or C_{9-12} cycloalkyl ring system radical and the like such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, indanyl, indenyl, 1,2,3,4-tetrahydro-naphthalenyl, 5,6,7,8-tetrahydro-naphthalenyl, 6,7,8,9-tetrahydro-*5H*-benzocycloheptenyl, 5,6,7,8,9,10-hexahydro-benzocyclooctenyl, fluorenyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, bicyclo[2.2.2]octyl, bicyclo[3.1.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octenyl, bicyclo[3.2.1]octenyl, adamantanyl, octahydro-4,7-methano-1*H*-indenyl, octahydro-2,5-methano-pentalenyl (also referred to as hexahydro-2,5-methano-pentalenyl) and the like. When further substituted, substituent variables may be placed on any ring carbon atom.

The term "heterocyclyl" means a saturated or partially unsaturated ring system radical, wherein at least one ring carbon atom has been replaced with one or more heteroatoms independently selected from N, O, S, S(O) or SO_2. A heterocyclyl ring system further includes a ring system having 1, 2, 3, or 4 carbon atom members replaced by a nitrogen atom. Alternatively, a ring may have 0, 1, 2, or 3 nitrogen atom members and 1 oxygen or sulfur atom member. Alternatively, up to two adjacent ring members may be heteroatoms, wherein one heteroatom is nitrogen and the other heteroatom is selected from N, S, or O.

Heterocyclyl typically includes, but is not limited to, furyl, thienyl, 2*H*-pyrrole, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, pyrrolyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2-imidazolinyl (also referred to as 4,5-dihydro-1*H*-imidazolyl), imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, tetrazolidinyl, 2*H*-pyran, 4*H*-pyran, pyridinyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl,

pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, azetidinyl, azepanyl, indolizinyl, indolyl, isoindolyl, 3*H*-indolyl, indolinyl (also referred to as 2,3-dihydro-indolyl), benzo[*b*]furyl, benzo[*b*]thienyl, 1*H*-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4*H*-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalzinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinuclidinyl, hexahydro-1,4-diazepinyl, 1,3-benzodioxolyl (also known as 1,3-methylenedioxyphenyl or benzo[1,3]dioxolyl), 2,3-dihydro-1,4-benzodioxinyl (also known as 1,4-ethylenedioxyphenyl), tetrahydro-furanyl, benzo-dihydro-furanyl, tetrahydro-pyranyl, benzo-tetrahydro-pyranyl, tetrahydro-thienyl, benzo-dihydro-thienyl, 5,6,7,8-tetrahydro-4*H*-cyclohepta(*b*)thienyl, 5,6,7-trihydro-4*H*-cyclohexa(*b*)thienyl, 5,6-dihydro-4*H*-cyclopenta(*b*)thienyl, tetrahydro-pyridazinyl, hexahydro-1,4-diazepinyl, hexahydro-1,4-oxazepanyl, 2,3-dihydro-1,4-benzodioxinyl, 2,3-dihydro-benzofuranyl 2-aza-bicyclo[2.2.1]heptyl, 1-aza-bicyclo[2.2.2]octyl, 8-aza-bicyclo[3.2.1]octyl, 7-oxa-bicyclo[2.2.1]heptyl and the like.

The term "aryl" means a monovalent, unsaturated aromatic hydrocarbon ring system radical. Aryl ring systems include phenyl, naphthalenyl, azulenyl, anthracenyl and the like.

The term "heteroaryl" means a monovalent, unsaturated aromatic hydrocarbon ring system radical, wherein at least one ring carbon atom has been replaced with one or more heteroatoms independently selected from N, O, S, S(O) or SO_2, as defined in heterocyclyl above. Heteroaryl ring systems include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, azaindolyl, isoindolyl, benzo[b]furanyl, benzo[b]thienyl, indazolyl, azaindazolyl, benzoimidazolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzothiadiazolyl, benzotriazolyl, purinyl, 4H-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalzinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl and the like.

The term "alkenyl-carbonyl" means a linking group of the formula: -alkenyl-C(O)-terminal group.

The term "alkenyl-sulfonyl" means a linking group of the formula: -alkenyl-SO_2-terminal group.

The term "amino" means a radical of the formula: $-NH_2$.

The term "aminoalkyl" means a radical of the formula: –NH–alkyl or $N(alkyl)_2$.

The term "aminosulfonylalkyl" means a radical of the formula: –NH–SO_2-alkyl or a linking group of the formula: -NH-SO_2-alkyl-terminal group.

The term "carbonyl" means a linking group of the formula: -C(O)-terminal group.

The term "halogen" means the group chloro, bromo, fluoro or iodo.

The term "sulfonylaminoalkyl" means a radical of the formula: –SO_2-NH-alkyl or –SO_2-N(alkyl)$_2$, or a linking group of the formula: -SO_2-NH-alkyl-terminal group.

The term "substituted" means one or more hydrogen atoms on a core molecule have been replaced with one or more radicals or linking groups, wherein the linking group, by definition is also further substituted. The ability of a particular radical or linking group to replace a hydrogen atom is optimally expected by one skilled to art to result in a chemically stable core molecule.

The term "dependently selected" means that the structure variables are specified in an indicated combination.

In general, IUPAC nomenclature rules are used throughout this disclosure.

Pharmaceutical Forms

The term "form" or "isolated form", in any context herein, means that certain compounds of the present invention may exist in various isolated states such as, without limitation, a salt, stereoisomer, crystalline, polymorph, amorphous, solvate, hydrate, ester, prodrug or metabolite form. The present invention encompasses all such compound forms and mixtures thereof, including active compounds in the form of essentially pure enantiomers, racemic mixtures, pure geometric isomers (such as *cis* and *trans* stereoisomers), mixtures of geometric isomers and tautomers.

The compounds of the present invention may be present in the form of pharmaceutically acceptable salts. For use in medicines, the "pharmaceutically acceptable salts" of the compounds of this invention refer to non-toxic acidic/anionic or basic/cationic salt forms.

Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or

phosphoric acid.

Furthermore when the compounds of the present invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

Thus, representative pharmaceutically acceptable salts include the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate (or camphosulfonate), carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, fumarate, gluconate, glutamate, hydrabamine, hydrobromine, hydrochloride, iodide, isothionate, lactate, malate, maleate, mandelate, mesylate, nitrate, oleate, pamoate, palmitate, phosphate/diphosphate, salicylate, stearate, sulfate, succinate, tartrate, tosylate.

The present invention includes within its scope prodrugs and metabolites of the compounds of this invention. In general, such prodrugs and metabolites will be functional derivatives of the compounds that are readily convertible *in vivo* into an active compound.

Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the means for treating, ameliorating or preventing a syndrome, disorder or disease described herein with a compound specifically disclosed or a compound, or prodrug or metabolite thereof, which would obviously be included within the scope of the invention albeit not specifically disclosed for certain of the instant compounds.

The term "prodrug" means a pharmaceutically acceptable form of a functional derivative of a compound of the invention (or a salt thereof), wherein the prodrug may be: 1) a relatively active precursor which converts *in vivo* to an active prodrug component; 2) a relatively inactive precursor which converts *in vivo* to an active prodrug component; or 3) a relatively less active component of the compound that contributes to therapeutic biological activity after becoming available *in vivo* (i.e., as a metabolite). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described in, for example, "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The term "metabolite" means a pharmaceutically acceptable form of a

metabolic derivative of a compound of the invention(or a salt thereof), wherein the derivative is a relatively less active component of the compound that contributes to therapeutic biological activity after becoming available *in vivo*.

The present invention contemplates compounds of various isomers and mixtures thereof. The term "isomer" refers to compounds that have the same composition and molecular weight but differ in a physical or chemical property, or both. Such substances have the same number and kind of atoms but differ in structure. The structural difference may be in constitution (geometric isomers) or in an ability to rotate the plane of polarized light (stereoisomers).

The term "stereoisomer" refers to isomers of identical constitution that differ in the arrangement of their atoms in space. Enantiomers and diastereomers are stereoisomers wherein an asymmetrically substituted carbon atom acts as a chiral center.

The term "chiral" refers to a molecule that is not superposable on its mirror image, implying the absence of an axis and a plane or center of symmetry. The term "enantiomer" refers to one of a pair of molecular species that are mirror images of each other and are not superposable. The term "diastereomer" refers to stereoisomers that are not related as mirror images. The symbols "*R*" and "*S*" represent the configuration of substituents around a chiral carbon atom(s). The symbols "*R**" and "*S**" denote the relative configurations of substituents around a chiral carbon atom(s).

The term "racemate" or "racemic mixture" refers to a compound of equimolar quantities of two enantiomeric species, wherein the compound is devoid of optical activity. The term "optical activity" refers to the degree to which a chiral molecule or nonracemic mixture of chiral molecules rotates the plane of polarized light.

The term "geometric isomer" means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Substituent atoms (other than hydrogen) on each side of a carbon-carbon double bond may be in an E or Z configuration. In the "E" configuration, the substituents are on opposite sides in relationship to the carbon-carbon double bond. In the "Z" configuration, the substituents are oriented on the same side in relationship to the carbon-carbon double bond.

The isomeric descriptors ("R," "S," "E," and "Z") indicate atom configurations relative to a core molecule and are intended to be used as defined in the literature.

The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include combining the free base (or free acid) of each isomer of an isomeric pair using an optically active acid (or base) to form an optically active salt (followed by fractional crystallization and regeneration of the free base), forming an ester or amide of each of the isomers of an isomeric pair by reaction with an appropriate chiral auxiliary (followed by fractional crystallization or chromatographic separation and removal of the chiral auxiliary), or separating an isomeric mixture of either an intermediate or a final product using various well known chromatographic methods.

Furthermore, compounds of the present invention may have one or more polymorph or amorphous crystalline forms and as such are intended to be included in the scope of the invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents (e.g., organic esters such as ethanolate and the like), and such are also intended to be encompassed within the scope of this invention.

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

Therapeutic Use

CB1 and CB2 cannabinoid receptors belong to the G-protein-coupled receptor (GCPR) family, a receptor super-family with a distinctive pattern of seven transmembrane domains, which inhibits N-type calcium channels and /or adenylate cyclase to inhibit Q-type calcium channels. CB1 receptors are present in the CNS, predominately expressed in brain regions associated with memory and movement such as the hippocampus (memory storage), cerebellum (coordination of motor function, posture and balance), basal ganglia (movement control), hypothalamus (thermal

regulation, neuroendocrine release, appetite), spinal cord (nociception), cerebral cortex (emesis) and periphery regions such as lymphoid organs (cell mediated and innate immunity), vascular smooth muscle cells (blood pressure), gastrointestinal tract (innate antiinflammatory in the tract and in the esophagus, duodenum, jejunum, ileum and colon, controlling esophageal and gastrointestinal motility), lung smooth muscle cells (bronchodilation), eye ciliary body (intraocular pressure).

CB2 receptors appear to be primarily expressed peripherally in lymphoid tissue (cell mediated and innate immunity), peripheral nerve terminals (peripheral nervous system), spleen immune cells (immune system modulation) and retina (intraocular pressure). CB2 mRNA is found in the CNS in cerebellar granule cells (coordinating motor function). Pharmacological and physiological evidence also suggests that there may be other cannabinoid receptor subtypes that have yet to be cloned and characterized.

Where activation or inhibition of a CB receptor appears to mediate various syndromes, disorders or diseases, potential areas of clinical application include, but are not limited to, controlling appetite, regulating metabolism, diabetes, reducing glaucoma-associated intraocular pressure, treating social and mood disorders, treating seizure-related disorders, treating substance abuse disorders, enhancing learning, cognition and memory, controlling organ contraction and muscle spasm, treating bowel disorders, treating respiratory disorders, treating locomotor activity or movement disorders, treating immune and inflammation disorders, regulating cell growth, use in pain management, use as a neuroprotective agent and the like or any combination thereof.

Thus, cannabinoid receptor modulators, including the compounds of the formula (I) or (Ia) of the present invention, are useful for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease including, but not limited to, controlling appetite, regulating metabolism, diabetes, glaucoma-associated intraocular pressure, pain, social and mood disorders, seizure-related disorders, substance abuse disorders, learning, cognition disorders, memory disorders, bowel disorders, respiratory disorders, locomotor activity disorders, movement disorders, immune disorders or inflammation disorders, controlling organ contraction and muscle spasm, enhancing learning, enhancing cognition, enhancing memory, regulating cell growth, providing neuroprotection and the like or any combination

thereof.

The present invention is directed to a method for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a compound of formula (I) or form thereof.

The present invention is further directed to a method for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a compound of formula (Ia) or form thereof.

The present invention is directed to a method for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject a combination product comprising an effective amount of a compound of formula (I) or formula (Ia) and a therapeutic agent.

Therapeutic agents contemplated for use in a combination product of the present invention include an anticonvulsant or a contraceptive agent. The anticonvulsant agents include, and are not limited to, topiramate, analogs of topiramate, carbamazepine, valproic acid, lamotrigine, gabapentin, phenytoin and the like and mixtures or pharmaceutically acceptable salts thereof. The contraceptive agents include, and are not limited to, such as progestin-only contraceptives and contraceptives that include both a progestin component and an estrogen component. The invention further includes a pharmaceutical composition wherein the contraceptive is an oral contraceptive, and wherein the contraceptive optionally includes a folic acid component.

The invention also includes a method of contraception in a subject comprising the step of administering to the subject a composition, wherein the composition comprises a contraceptive and a CB1 receptor inverse-agonist or antagonist compound of formulae (I) or (Ia), wherein the composition either reduces the urge to smoke in the subject or assists the subject in losing weight, or both.

The present invention includes cannabinoid receptor modulators useful for treating, ameliorating or preventing a CB receptor mediated syndrome, disorder or disease. The usefulness of a compound of the present invention or composition thereof as a CB modulator can be determined according to the methods disclosed herein. The

scope of such use includes treating, ameliorating or preventing a plurality of CB receptor mediated syndromes, disorders or diseases.

The present invention is also directed to a method for treating, ameliorating or preventing a CB receptor mediated syndrome, disorder or disease in a subject in need thereof wherein the syndrome, disorder or disease is related to appetite, metabolism, diabetes, glaucoma-associated intraocular pressure, social and mood disorders, seizures, substance abuse, learning, cognition or memory, organ contraction or muscle spasm, bowel disorders, respiratory disorders, locomotor activity or movement disorders, immune and inflammation disorders, unregulated cell growth, pain management, neuroprotection and the like.

A compound of formulae (I) or (Ia) for use as a CB receptor modulator includes a compound having a mean inhibition constant (IC_{50}) for CB receptor binding activity of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 15 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 0.1 nM.

A compound of formulae (I) or (Ia) for use as a CB receptor modulator of the invention includes a compound having a CB1 agonist IC_{50} for CB1 agonist binding activity of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 15 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 0.1 nM.

A compound of formulae (I) or (Ia) for use as a CB receptor modulator of the invention includes a compound having a CB1 antagonist IC_{50} for CB1 antagonist binding activity of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 15 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01

nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 0.1 nM.

A compound of formulae (I) or (Ia) for use as a CB receptor modulator of the invention includes a compound having a CB1 inverse-agonist IC_{50} for CB1 inverse-agonist binding activity of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 15 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 0.1 nM.

A compound of formulae (I) or (Ia) for use as a CB receptor modulator of the invention includes a compound having a CB2 agonist IC_{50} for CB2 agonist binding activity of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 15 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 0.1 nM.

A compound of formulae (I) or (Ia) for use as a CB receptor modulator of the invention includes a compound having a CB2 antagonist IC_{50} for CB2 antagonist binding activity of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 15 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 0.1 nM.

A compound of formulae (I) or (Ia) for use as a CB receptor modulator of the invention includes a compound having a CB2 inverse-agonist IC_{50} for CB2 inverse-agonist binding activity of between about 50 μM to about 0.01 nM; between about 25 μM to about 0.01 nM; between about 15 μM to about 0.01 nM; between about 10 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to

about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 0.1 nM.

The term "cannabinoid receptor" refers to any one of the known or heretofore unknown subtypes of the class of cannabinoid receptors that may be bound by a cannabinoid modulator compound of the present invention; in particular, a cannabinoid receptor selected from the group consisting of a CB1 receptor and a CB2 receptor. The term "modulator" further refers to the use of a compound of the invention as a CB receptor agonist, antagonist or inverse-agonist.

The present invention includes a method for treating, ameliorating or preventing a CB receptor mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a compound of the present invention or composition thereof, wherein the cannabinoid receptor is a CB1 or CB2 receptor; and, the compound is an agonist, antagonist or inverse-agonist of the receptor.

The present invention includes a method for treating, ameliorating or preventing a CB receptor mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a compound of the present invention in a combination product with a therapeutic agent such as an anticonvulsant or contraceptive agent or composition thereof, wherein the cannabinoid receptor is a CB1 or CB2 receptor; and, the compound is an agonist, antagonist or inverse-agonist of the receptor.

It should be understood that contraceptive agents suitable for use in a combination product are not limited to oral contraceptives, but also include other commonly available contraceptives such as those that are administered transdermally, by injection or via implant.

Except as further specified, "combination product" means a pharmaceutical composition comprising a compound of formulae (I) or (Ia) in combination with one or more therapeutic agents. The dosages of the compound of formula (I) or (Ia) and the one or more therapeutic agents are adjusted when combined to achieve an effective amount.

The term "subject" as used herein, refers to a patient, which may be an animal, or a mammal or a human, which has been the object of treatment, observation or experiment and is at risk of (or susceptible to) developing a CB receptor mediated

syndrome, disorder or disease.

The term "administering" is to be interpreted in accordance with the methods of the present invention. Such methods include therapeutically or prophylactically administering an effective amount of a composition or medicament of the present invention at different times during the course of a therapy or concurrently as a product in a combination form.

Prophylactic administration can occur prior to the manifestation of symptoms characteristic of a CB receptor mediated syndrome, disorder or disease such that the syndrome, disorder or disease is treated, ameliorated, prevented or otherwise delayed in its progression. The methods of the present invention are further to be understood as embracing all therapeutic or prophylactic treatment regimens used by those skilled in the art.

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

The effective amount of an instant compound of the invention is from about 0.001 mg/kg/day to about 300 mg/kg/day.

Wherein the present invention is directed to the administration of a combination of a compound of formula (I) and an anticonvulsant or contraceptive agent, the term "effective amount" means that amount of the combination of agents taken together so that the combined effect elicits the desired biological or medicinal response.

As those skilled in the art will appreciate, the effective amounts of the components comprising the combination product may be independently optimized and combined to achieve a synergistic result whereby the pathology is reduced more than it would be if the components of the combination product were used alone.

For example, the effective amount of a combination product comprising administration of a compound of formula (I) and topiramate would be the amount of the compound of formula (I) and the amount of topiramate that when taken together or sequentially have a combined effect that is effective. Further, it will be recognized by one skilled in the art that in the case of combination product with an effective amount, as in the example above, the amount of either or both the compound of formula (I) or

the anticonvulsant (e.g., topiramate) individually may or may not be effective.

Wherein the present invention is directed to the administration of a combination product, the instant compound and the anticonvulsant or contraceptive agent may be co-administered by any suitable means, simultaneously, sequentially or in a single pharmaceutical composition. Where the instant compound(s) and the anticonvulsant or contraceptive agent components are administered separately, the number of dosages of each compound(s) given per day, may not necessarily be the same, e.g. where one compound may have a greater duration of activity, and will therefore, be administered less frequently.

The compound(s) of formula (I) and the anticonvulsant(s) or contraceptive agent(s) may be administered via the same or different routes of administration. The compound(s) of formula (I) and the anticonvulsant(s) or contraceptive agent(s) may be administered via the same or different routes of administration.

Suitable examples of methods of administration are orally, intravenous (iv), intramuscular (im), and subcutaneous (sc). Compounds may also be administrated directly to the nervous system including, but not limited to the intracerebral, intraventricular, intracerebroventricular, intrathecal, intracisternal, intraspinal or peri-spinal routes and the like or any combination thereof, or by delivery via intracranial or intravertebral needles and/or catheters with or without pump devices and the like or any combination thereof.

The compound(s) of formula (I) and the anticonvulsant(s) or contraceptive agent(s) may be administered according to simultaneous or alternating regimens, at the same or different times during the course of the therapy, concurrently in divided or single forms.

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

The term "CB receptor mediated syndrome, disorder, or disease" refers to syndromes, disorders or diseases associated with a biological response mediated by a CB receptor such that there is discomfort or decreased life expectancy to the organism.

CB receptor mediated syndromes, disorders or diseases can occur in both animals and humans and include appetite, metabolism, diabetes, obesity, glaucoma-associated intraocular pressure, social, mood, seizure, substance abuse, learning, cognition, memory, organ contraction, muscle spasm, bowel, respiratory, locomotor activity, movement, immune, inflammation, cell growth, pain or neurodegenerative related syndromes, disorders or diseases.

Appetite related syndromes, disorders or diseases include obesity, overweight condition, anorexia, bulimia, cachexia, dysregulated appetite and the like.

Obesity related syndromes, disorders or diseases include obesity as a result of genetics, diet, food intake volume, metabolic syndrome, disorder or disease, hypothalmic disorder or disease, age, reduced activity, abnormal adipose mass distribution, abnormal adipose compartment distribution and the like.

Metabolism related syndromes, disorders or diseases include metabolic syndrome, dyslipidemia, elevated blood pressure, diabetes, insulin sensitivity or resistance, hyperinsulinemia, hypercholesterolemia, hyperlipidemias, hypertriglyceridemias, atherosclerosis, hepatomegaly, steatosis, abnormal alanine aminotransferase levels, inflammation, atherosclerosis and the like.

Diabetes related syndromes, disorders or diseases include glucose dysregulation, insulin resistance, glucose intolerance, hyperinsulinemia, dyslipidemia, hypertension, obesity and the like.

Type II diabetes mellitus (non-insulin-dependent diabetes mellitus) is a metabolic disorder (i.e., a metabolism related syndrome, disorder or disease) in which glucose dysregulation and insulin resistance results in chronic, long-term medical complications for both adolescents and adults affecting the eyes, kidneys, nerves and blood vessels and can lead to blindness, end-stage renal disease, myocardial infarction or limb amputation and the like. Glucose dysregulation includes the inability to make sufficient insulin (abnormal insulin secretion) and the inability to effectively use insulin (resistance to insulin action in target organs and tissues). Individuals suffering from Type II diabetes mellitus have a relative insulin deficiency. That is, in such individuals, plasma insulin levels are normal to high in absolute terms, although they are lower than predicted for the level of plasma glucose that is present.

Type II diabetes mellitus is characterized by the following clinical signs or symptoms: persistently elevated plasma glucose concentration or hyperglycemia;

polyuria; polydipsia and / or polyphagia; chronic microvascular complications such as retinopathy, nephropathy and neuropathy; and macrovascular complications such as hyperlipidemia and hypertension. These micro-and macro-vascular complications can lead to blindness, end-stage renal disease, limb amputation and myocardial infarction.

Insulin Resistance Syndrome (IRS) (also referred to as Syndrome X, Metabolic Syndrome or Metabolic Syndrome X) is a disorder that presents risk factors for the development of Type II diabetes and cardiovascular disease including glucose intolerance, hyperinsulinemia, insulin resistance, dyslipidemia (e.g. high triglycerides, low HDL-cholesterol and the like), hypertension and obesity.

Social or mood related syndromes, disorders or diseases include depression, anxiety, psychosis, social affective disorders or cognitive disorders and the like.

Substance abuse related syndromes, disorders or diseases include drug abuse, drug withdrawal, alcohol abuse, alcohol withdrawal, nicotine withdrawal, cocaine abuse, cocaine withdrawal, heroin abuse, heroin withdrawal and the like.

Learning, cognition or memory related syndromes, disorders or diseases include memory loss or impairment as a result of age, disease, side effects of medications (adverse events) and the like.

Muscle spasm syndromes, disorders or diseases include multiple sclerosis, cerebral palsy and the like.

Locomotor activity and movement syndromes, disorders or diseases include stroke, Parkinson's disease, multiple sclerosis, epilepsy and the like.

Bowel related syndromes, disorders or diseases include bowel dysmotility associated disorders (either accompanied by pain, diarrhea or constipation or without), irritable bowel syndrome (and other forms of bowel dysmotility and the like), inflammatory bowel diseases (such as ulcerative colitis, Crohn's disease and the like) and celiac disease.

Respiratory related syndromes, disorders or diseases include chronic pulmonary obstructive disorder, emphysema, asthma, bronchitis and the like.

Immune or inflammation related syndromes, disorders or diseases include allergy, rheumatoid arthritis, dermatitis, autoimmune disease, immunodeficiency, chronic neuropathic pain and the like.

Cell growth related syndromes, disorders or diseases include dysregulated mammalian cell proliferation, breast cancer cell proliferation, prostrate cancer cell

proliferation and the like.

Pain related syndromes, disorders or diseases include central and peripheral pathway mediated pain, bone and joint pain, migraine headache associated pain, cancer pain, menstrual cramps, labor pain and the like.

Neurodegenerative related syndromes, disorders or diseases include Parkinson's Disease, multiple sclerosis, epilepsy, ischemia or secondary biochemical injury collateral to traumatic head or brain injury, brain inflammation, eye injury or stroke and the like.

The present invention includes a method for treating, ameliorating or preventing a cannabinoid receptor agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a cannabinoid agonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a cannabinoid receptor agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a cannabinoid agonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a cannabinoid receptor inverse-agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a cannabinoid inverse-agonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a cannabinoid receptor inverse-agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a cannabinoid inverse-agonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a cannabinoid receptor inverse-agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a cannabinoid inverse-agonist compound of the present invention in a combination product with one or more contraceptives or composition thereof.

The present invention includes a method for treating, ameliorating or preventing

a cannabinoid receptor antagonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a cannabinoid antagonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a cannabinoid receptor antagonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a cannabinoid antagonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a cannabinoid receptor antagonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject a therapeutically or prophylactically effective amount of a cannabinoid antagonist compound of the present invention in a combination product with one or more contraceptives or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 agonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 agonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 inverse-agonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 inverse-agonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing

a CB1 receptor inverse-agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 inverse-agonist compound of the present invention in a combination product with one or more contraceptives or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated appetite related obesity related or metabolism related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 inverse-agonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated appetite related obesity related or metabolism related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 inverse-agonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated appetite related obesity related or metabolism related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 inverse-agonist compound of the present invention in a combination product with one or more contraceptives or composition thereof.

Appetite related syndromes, disorders or diseases include obesity, overweight condition, anorexia, bulimia, cachexia, dysregulated appetite and the like.

Obesity related syndromes, disorders or diseases include obesity as a result of genetics, diet, food intake volume, metabolic syndrome, disorder or disease, hypothalmic disorder or disease, age, reduced activity, abnormal adipose mass distribution, abnormal adipose compartment distribution and the like.

Metabolism related syndromes, disorders or diseases include metabolic syndrome, dyslipidemia, elevated blood pressure, diabetes, insulin sensitivity or resistance, hyperinsulinemia, hypercholesterolemia, hyperlipidemias, hypertriglyceridemias, atherosclerosis, hepatomegaly, steatosis, abnormal alanine aminotransferase levels, inflammation, atherosclerosis and the like.

The present invention includes a method for treating, ameliorating or preventing

a CB1 receptor antagonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 antagonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor antagonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 antagonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB1 receptor antagonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 antagonist compound of the present invention in a combination product with one or more contraceptives or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB2 receptor agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB2 agonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB2 receptor agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB2 agonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes include a method for treating, ameliorating or preventing a CB2 receptor inverse-agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB2 inverse-agonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB2 receptor inverse-agonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB2 inverse-agonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing

a CB2 receptor antagonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB2 antagonist compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a CB2 receptor antagonist mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB2 antagonist compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a metabolism related syndrome, disorder or disease, an appetite related syndrome, disorder or disease, a diabetes related syndrome, disorder or disease, an obesity related syndrome, disorder or disease or a learning, cognition or memory related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a compound of the present invention or composition thereof.

The present invention includes a method for treating, ameliorating or preventing a metabolism related syndrome, disorder or disease, an appetite related syndrome, disorder or disease, a diabetes related syndrome, disorder or disease, an obesity related syndrome, disorder or disease or a learning, cognition or memory related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a compound of the present invention in a combination product with an anticonvulsant or composition thereof.

The present invention includes a pharmaceutical composition or medicament comprising an admixture of a compound of the present invention and an optional pharmaceutically acceptable carrier.

The present invention includes a pharmaceutical composition or medicament comprising an admixture of two or more compounds of the present invention and an optional pharmaceutically acceptable carrier.

The present invention also includes a pharmaceutical composition or medicament comprising an admixture of a compound of formula (I), an anticonvulsant and an optional pharmaceutically acceptable carrier.

Such pharmaceutical compositions are particularly useful for treating a subject suffering from a metabolism related syndrome, disorder or disease, an appetite related

syndrome, disorder or disease, a diabetes related syndrome, disorder or disease, an obesity related syndrome, disorder or disease, or a learning, cognition or memory related syndrome, disorder or disease.

Anticonvulsants useful in the methods and compositions of the present invention in combination with a compound of formula (I) or (Ia) include, but are not limited to, topiramate, analogs of topiramate, carbamazepine, valproic acid, lamotrigine, gabapentin, phenytoin and the like and mixtures or pharmaceutically acceptable salts thereof.

Topiramate, 2,3:4,5-bis-O-(1-methylethylidene)-ß-D-fructopyranose sulfamate, is currently marketed for the treatment of seizures in patients with simple and complex partial epilepsy and seizures in patients with primary or secondary generalized seizures in the United States, Europe and most other markets throughout the world. Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent, and as 15 mg and 25 mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food. U.S. Patent No. 4,513,006, incorporated herein by reference, discloses topiramate and analogs of topiramate, their manufacture and use for treating epilepsy. Additionally, topiramate may also be made by the process disclosed in US Patent Nos. 5,242,942 and 5,384,327, which are incorporated by reference herein. The term "analogs of topiramate", as used herein, refers to the sulfamate compounds of formula (I), which are disclosed in U.S. Patent No. 4,513,006 (*see, e.g.*, column 1, lines 36-65 of U.S. 4,513,006).

For use in the methods of the present invention in combination with a compound of the formula (I) or (Ia), topiramate (or an analog of topiramate) can be administered in the range of about 10 to about 1000 mg daily, preferably in the range of about 10 to about 650 mg daily, more preferably in the range of about 15 to about 325 mg once or twice daily.

Carbamazepine, 5*H*-dibenz[*b,f*]azepine-5-carboxamide, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, XR (extended release) tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5 mL (teaspoon); U.S. Patent No. 2,948,718, herein incorporated by reference in its entirety, discloses carbamazepine and its methods of use.

For use in the methods of the present invention in combination with a

compound of the formula (I) or (Ia), carbamazepine can be administered in the range of about 200 to about 1200 mg/day; preferably, about 400 mg/day.

Valproic acid, 2-propylpentanoic acid or dipropylacetic acid, is an antiepileptic agent commercially available as soft elastic capsules containing 250 mg valproic acid, and as syrup containing the equivalent of 250 mg valproic acid per 5 mL as the sodium salt. Valproic acid and various pharmaceutically acceptable salts are disclosed in U.S. Patent No. 4,699,927, which is incorporated by reference herein in its entirety.

For use in the methods of the present invention in combination with a compound of the formula (I) or (Ia), valproic acid can be administered in the range of about 250 to about 2500 mg/day; preferably, about 1000 mg/day.

Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, is an antiepileptic drug commercially available for oral administration as tablets containing 25 mg, 100 mg, 150 mg, and 200 mg of lamotrigine, and as chewable dispersible tablets containing 2 mg, 5 mg, or 25 mg of lamotrigine. Lamotrigine and its uses are disclosed in U.S. Patent No. 4,486,354, incorporated by reference herein in its entirety.

For use in the methods of the present invention in combination with a compound of the formula (I) or (Ia), lamotrigine can be administered in the range of about 50 to about 600 mg/day in one to two doses; preferably, about 200 to about 400 mg/day; most preferably, about 200 mg/day.

Gabapentin, 1-(aminomethyl)cyclohexaneacetic acid, is commercially available for the adjunctive treatment of epilepsy and for postherpetic neuralgia in adults as capsules containing 100 mg, 300 mg, and 400 mg of gabapentin, film-coated tablets containing 600 mg and 800 mg of gabapentin, and an oral solution containing 250 mg/5 mL of gabapentin. Gabapentin and its methods of use are described in U.S. Patent No. 4,024,175 and 4,087,544, herein incorporated by reference in their entirety.

For use in the methods of the present invention in combination with a compound of the formula (I) or (Ia), gabapentin can be administered in the range of about 300 to about 3600 mg/day in two to three divided doses; preferably, about 300 to about 1800 mg/day; most preferably, about 900 mg/day.

Phenytoin sodium, 5,5-diphenylhydantoin sodium salt, is an anticonvulsant, which is commercially available for oral administration as capsules containing 100 mg, 200 mg or 300 mg of phenytoin sodium.

For use in the methods of the present invention in combination with a

compound of the formula (I) or (Ia), phenytoin sodium can be administered in the range of about 100 to about 500 mg/day; preferably, about 300 to about 400 mg/day; most preferably, about 300 mg/day.

The present invention also includes a pharmaceutical composition or medicament comprising an admixture of a compound of formula (I) or (Ia), one or more contraceptives and an optional pharmaceutically acceptable carrier.

Contraceptives suitable for use in a combination product include, for example, ORTHO CYCLEN®, ORTHO TRI-CYCLEN®, ORTHO TRI-CYCLEN LO®, and ORTHO EVRA®, all available from Ortho-McNeil Pharmaceutical, Inc., Raritan, NJ. It should also be understood that contraceptives suitable for use in the invention encompass those contraceptives that include a folic acid component.

Both smoking and obesity have been identified as risk factors in women taking oral contraceptives. CB1 receptor antagonists and inverse agonists have been found to be useful therapeutic agents for reducing the urge to smoke and for assisting patients with eating disorders to lose weight.

Accordingly, the invention further includes a method of reducing the risk factors associated with either smoking or obesity or both for women taking contraceptives by co-administering with a contraceptive at least one of a CB1 receptor antagonist of formula (I) or (Ia) or a CB1 receptor inverse-agonist compound of formula (I) or (Ia) or a mixture thereof.

The use of such compounds or a pharmaceutical composition or medicament thereof is to either reduce the desire to smoke or assist in weight loss for patients taking contraceptives or both.

Pharmaceutical Compositions

The term "composition" refers to a product comprising the specified ingredients in the specified amounts, as well as any product that results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. The invention further comprises mixing one or more of the compounds of the invention and a pharmaceutically acceptable carrier; and, includes those compositions resulting from such a process. Contemplated processes include both traditional and modern pharmaceutical techniques.

Pharmaceutical compositions of the invention may, alternatively or in addition

to a compound of formula (I) or (Ia), comprise a pharmaceutically acceptable salt of a compound of formula (I) or (Ia) or a prodrug or pharmaceutically active metabolite of such a compound or salt in admixture with a pharmaceutically acceptable carrier.

The term "medicament" refers to a product for use in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease.

"Pharmaceutically acceptable carrier" means molecular entities and compositions that are of sufficient purity and quality for use in the formulation of a composition of the invention and that, when appropriately administered to an animal or a human, do not produce an adverse, allergic, or other untoward reaction.

Since both clinical and veterinary uses are equally included within the scope of the present invention, a pharmaceutically acceptable formulation would include a composition or medicament formulation for either clinical or veterinary use.

The present invention includes a process for making the composition or medicament comprising mixing any of the instant compounds and a pharmaceutically acceptable carrier and include those compositions or medicaments resulting from such a process. Contemplated processes include both conventional and unconventional pharmaceutical techniques. Other examples include a composition or medicament comprising a mixture of at least two of the instant compounds in association with a pharmaceutically acceptable carrier.

The composition or medicament may be administered in a wide variety of dosage unit forms depending on the method of administration; wherein such methods include (without limitation) oral, sublingual, nasal (inhaled or insufflated), transdermal, rectal, vaginal, topical (with or without occlusion), intravenous (bolus or infusion) or for injection (intraperitoneally, subcutaneously, intramuscularly, intratumorally or parenterally) using a suitable dosage form well known to those of ordinary skill in the area of pharmaceutical administration. Accordingly, the term "dosage unit" or "dosage form" is alternatively used to refer to (without limitation) a tablet, pill, capsule, solution, syrup, elixir, emulsion, suspension, suppository, powder, granule or sterile solution, emulsion or suspension (for injection from an ampoule or using a device such as an auto-injector or for use as an aerosol, spray or drop). Furthermore, the composition may be provided in a form suitable for weekly or monthly administration (e.g. as an insoluble salt of the active compound (such as the decanoate salt) adapted to provide a depot preparation for intramuscular injection).

In preparing a dosage form, the principal active ingredient (such as a compound of the present invention or a pharmaceutically acceptable salt, racemate, enantiomer, or diastereomer thereof) is optionally mixed with one or more pharmaceutical carriers (such as a starch, sugar, diluent, granulating agent, lubricant, glidant, binder, disintegrating agent and the like), one or more inert pharmaceutical excipients (such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, syrup and the like), one or more conventional tableting ingredient (such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate, any of a variety of gums and the like) and a diluent (such as water and the like) to form a homogeneous composition (whereby the active ingredient is dispersed or suspended evenly throughout the mixture) which may be readily subdivided into dosage units containing equal amounts of a compound of the present invention.

Binders include, without limitation, starch, gelatin, natural sugars (such as glucose, beta-lactose and the like), corn sweeteners and natural and synthetic gums (such as acacia, tragacanth, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like). Disintegrating agents include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Because of the ease of administration, tablets and capsules represent an advantageous oral dosage unit form, wherein solid pharmaceutical carriers are employed. If desired, tablets may be sugar or film coated or enteric-coated by standard techniques. Tablets may also be coated or otherwise compounded to provide a prolonged therapeutic effect. For example, the dosage form may comprise an inner dosage and an outer dosage component, whereby the outer component is in the form of an envelope over the inner component. The two components may further be separated by a layer, which resists disintegration in the stomach (such as an enteric layer) and permits the inner component to pass intact into the duodenum or a layer which delays or sustains release. A variety of enteric and nonenteric layer or coating materials may be used (such as polymeric acids, shellacs, acetyl alcohol, cellulose acetate and the like) or combinations thereof.

The liquid forms in which a compound of the present invention may be incorporated for oral administration include (without limitation), aqueous solutions, suitably flavored syrups, aqueous or oil suspensions (using a suitable synthetic or natural gum dispersing or suspending agent such as tragacanth, acacia, alginate,

dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone, gelatin and the like), flavored emulsions (using a suitable edible oil such as cottonseed oil, sesame oil, coconut oil, peanut oil and the like), elixirs and other similar liquid forms with a variety of pharmaceutically acceptable vehicles.

As is also known in the art, the compounds may alternatively be administered parenterally via injection. For parenteral administration, sterile solutions or injectable suspensions may be parenteral vehicles wherein appropriate liquid carriers, suspending agents and the like are employed. Sterile solutions are a preferred parenteral vehicle. Isotonic preparations that generally contain suitable preservatives are employed when intravenous administration is desired. A parenteral formulation may consist of the active ingredient dissolved in or mixed with an appropriate inert liquid carrier. Acceptable liquid carriers comprise aqueous solvents and the like and other optional ingredients for aiding solubility or preservation. Such aqueous solvents include sterile water, Ringer's solution or an isotonic aqueous saline solution. Alternatively, a sterile non-volatile oil may be employed as a solvent agent. Other optional ingredients include vegetable oils (such as peanut oil, cottonseed oil, sesame oil and the like), organic solvents (such as solketal, glycerol, formyl and the like), preservatives, isotonizers, solubilizers, stabilizers, pain-soothing agents and the like. A parenteral formulation is prepared by dissolving or suspending the active ingredient in the liquid carrier whereby the final dosage unit contains from 0.005 to 10% by weight of the active ingredient.

Compounds of the present invention may be administered intranasally using a suitable intranasal vehicle. Compounds of the present invention may be administered topically using a suitable topical transdermal vehicle or a transdermal patch. Administration via a transdermal delivery system requires a continuous rather than intermittent dosage regimen.

Compounds of the present invention may also be administered via a rapid dissolving or a slow release composition, wherein the composition includes a biodegradable rapid dissolving or slow release carrier (such as a polymer carrier and the like) and a compound of the invention. Rapid dissolving or slow release carriers are well known in the art and are used to form complexes that capture therein an active compound(s) and either rapidly or slowly degrade/dissolve in a suitable environment (e.g., aqueous, acidic, basic, etc). Such particles are useful because they degrade/dissolve in body fluids and release the active compound(s) therein. The

particle size of a compound of the present invention, carrier or any excipient used in such a composition may be optimally adjusted using techniques known to those of ordinary skill in the art.

The present invention includes a composition of an instant compound or prodrug thereof present in a prophylactically or therapeutically effective amount necessary for symptomatic relief to a subject in need thereof. A prophylactically or therapeutically effective amount of an instant compound or prodrug thereof may range from about 0.01 ng to about 1 g and may be constituted into any form suitable for the administration method and regimen selected for the subject.

Depending on the subject and disease to be treated, the prophylactically or therapeutically effective amount for a person of average body weight of about 70 kg per day may range from about 0.01 ng/kg to about 300 mg/kg; from about 0.1 ng/kg to about 200 mg/kg; from about 0.5 ng/kg to about 100 mg/kg; or, from about 0.1 ng/kg to about 50 mg/kg.

An optimal prophylactically or therapeutically effective amount and administration method and regimen may be readily determined by those skilled in the art, and will vary depending on factors associated with the particular patient being treated (age, weight, diet and time of administration), the severity of the condition being treated, the compound and dosage unit being employed, the mode of administration and the strength of the preparation.

Dosage unit(s) may be administered to achieve the therapeutically or prophylactically effective amount in a regimen of from about once per day to about 5 times per day. The preferred dosage unit for oral administration is a tablet containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 or 500 mg of the active ingredient.

Representative compounds for use in the therapeutic methods and pharmaceutical compositions described herein include compounds selected from:

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (hexahydro-cyclopenta[c]pyrrol-2-yl)-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-pyridin-2-yl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid (4-hydroxy-piperidin-1-yl)-amide,

1-{[5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carbonyl]-amino}-1-methyl-piperidinium,

1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide, and

1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide.

Synthetic Methods

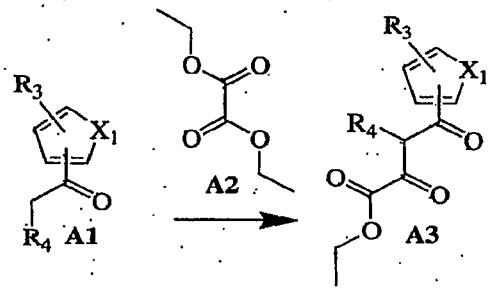
Representative compounds of the present invention can be synthesized in accordance with the general synthetic schemes described below and are illustrated more particularly in the specific synthetic examples that follow. The general schemes and specific examples are offered by way of illustration; the invention should not be construed as being limited by the chemical reactions and conditions expressed. The methods for preparing the various starting materials used in the schemes and examples are well within the skill of persons versed in the art. No attempt has been made to optimize the yields obtained in any of the example reactions. One skilled in the art

would know how to increase such yields through routine variations in reaction times, temperatures, solvents or reagents.

The terms used in describing the invention are commonly used and known to those skilled in the art. When used herein, the following abbreviations and formulae have the indicated meanings:

Cpd	compound
$(Boc)_2O$	di-*tert*-butyldicarbonate
EtOAc	ethyl acetate
Et_2O	anhydrous ether
K_2CO_3	potassium carbonate
KOtBu	potassium tert-butoxide
LHMDS or LiHMDS	lithium bis(trimethylsilyl)amide
min(s)/hr(s)	minute(s)/hour(s)
RT/rt/r.t.	room temperature
$SOCl_2$	thionyl chloride
TEA or Et_3N	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Scheme A

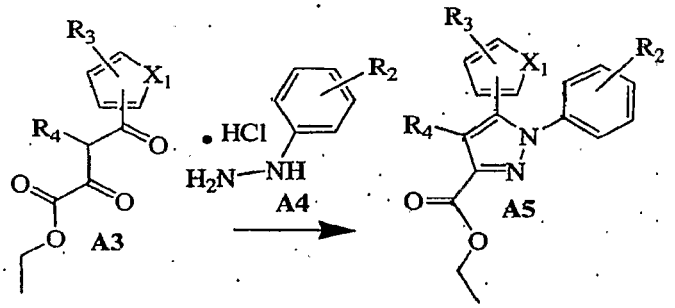


A solution of Compound **A1** (in a solvent such as Et_2O, THF and the like or a mixture thereof) in a reagent solution (such as LHMDS and the like in a solvent such as Et_2O or THF and the like or a mixture thereof) is reacted with a solution of Compound **A2** (in a solvent such as Et_2O and the like) to yield a Compound **A3**.

The oxalic acid diethyl ester Compound **A2** is used by way of illustration in this scheme; the scope of compounds representative of the present invention should not be construed as being limited to the use of oxalic acid diethyl ester or by the unsubstituted diethyl ester portions of Compound **A2**.

The present invention includes compounds prepared using other esters such as

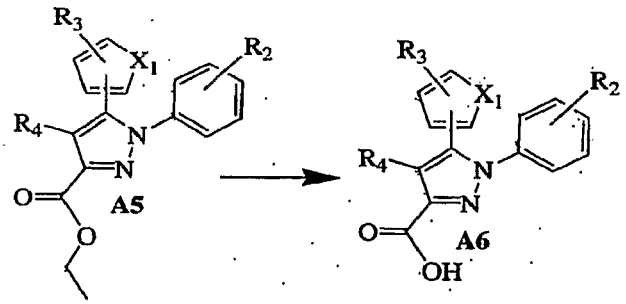
dimethoxy-acetic acid methyl ester and the like or esters which are further substituted in place of Compound **A2** using techniques known to those skilled in the art.



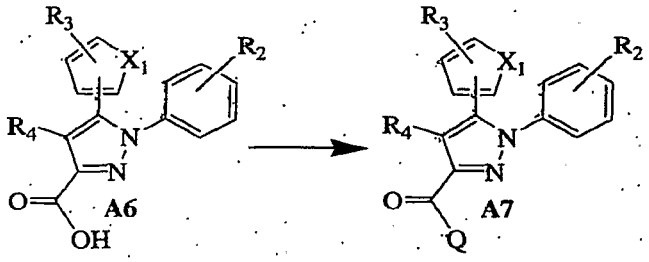
A solution of Compound **A3** (in a solvent such as one or more of MeOH, EtOH, CH_2Cl_2 and the like) is reacted with a substituted phenyl hydrazine mono or dihydrochloride Compound **A4** to provide a Compound **A5**.

The hydrazine hydrochloride or dihydrochloride Compound **A4** may be converted to the free base by methods known to those skilled in the art. In the examples of the present invention, the free base is prepared either in situ (as shown for illustrative purposes in this Scheme) or separately (then added to the reaction mixture) by reaction with K_2CO_3.

As illustrated in this Scheme, Compound **A4** may also be further substituted with a variety of R_2 substituents (as defined herein). In many instances, the substituted hydrazine Compound **A4** is commercially available. When not commercially available, a particularly substituted Compound **A4** may be prepared by methods known to those skilled in the art.

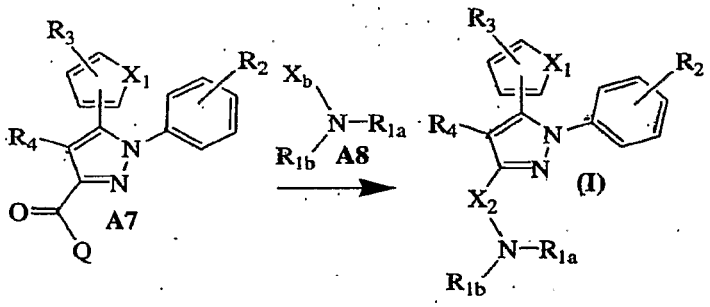


Compound **A5** is reacted in a reagent solution (such as LiOH or NaOH in a solvent such as a mixture of THF, ethanol and water and the like) to provide a Compound **A6**.



Compound **A6** is reacted in a reagent solution (such as $SOCl_2$ and the like in a solvent such as CH_2Cl_2 and the like) at reflux temperature to provide a Compound **A7.** As a result of this illustrative reaction, Q represents a halogen atom leaving group.

The product of another illustrative reaction includes a Compound **A7** wherein Q is a hydrogen atom. Such a product is obtained by reacting Compound **A1** with dimethoxy-acetic acid methyl ester in place of oxalic acid diethyl ester Compound **A2** using techniques known to those skilled in the art.



A solution of Compound **A7** (in a suitable solvent) is reacted with a solution of a Compound **A8** (in a suitable solvent) to provide a compound of formula (I).

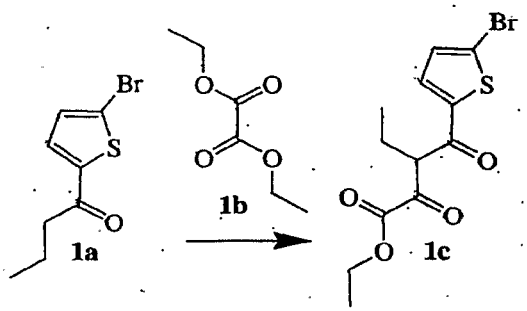
When Q is a halogen atom, the X_b portion of Compound **A8** is hydrogen. As a result, X_2 in formula (I) is carbonyl.

When Q is a hydrogen atom, the X_b portion of Compound **A8** is an alkyl-sulfonyl moiety or an alkyl-carbonyl moiety. As a result, X_2 in formula (I) is alkenyl-sulfonyl or alkenyl-carbonyl.

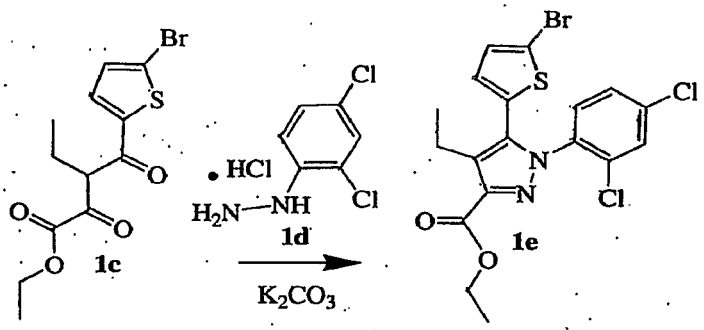
The synthetic examples that follow herein describe more completely the preparation of particular compounds included within the scope of the present invention.

Example 1

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide (Cpd 35)

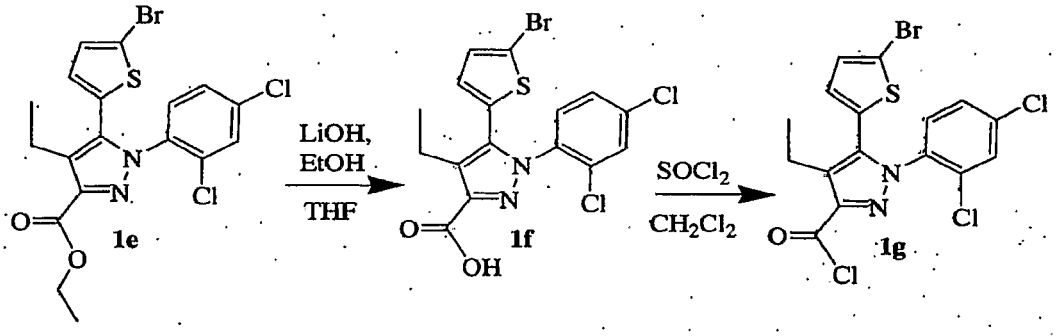


A solution of 1-(5-bromo-thiophen-2-yl)-butan-1-one Compound **1a** (2.8 g, 12 mmol) in THF (20 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (14.4 mL of 1.0M solution in THF) in THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 2 hrs. Diethyl oxalate Compound **1b** (1.63 mL, 12 mmol) in THF (10 mL) was added slowly to the mixture at -78 °C. The mixture was stirred at -78 °C for 1 hr, allowed to gradually warm up to room temperature and stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with 1N HCl (1×100 mL) and water (1×100 mL). The organic layer was dried over sodium sulfate, then filtered and concentrated to give 3-(5-bromo-thiophene-2-carbonyl)-2-oxo-pentanoic acid ethyl ester Compound **1c** (3.2 g, 80.2%) as an orange oil, which was used in the next step without further purification.



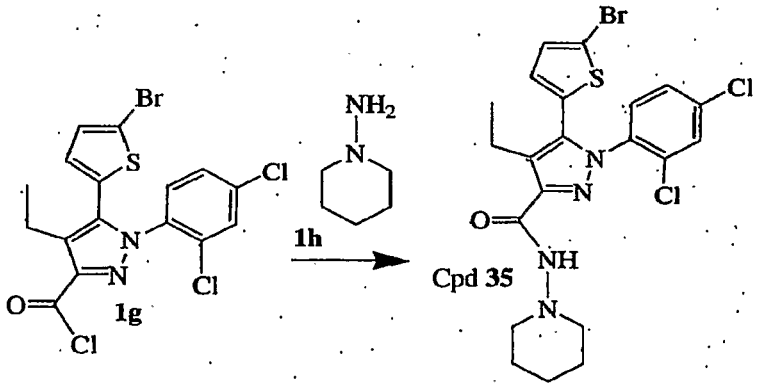
Anhydrous (2,4-dichloro-phenyl)-hydrazine hydrochloride Compound **1d** (1.06 g, 5 mmol) and K_2CO_3 (0.69 g, 5 mmol) were added to a solution of Compound **1c** (1.67 g, 5 mmol) in ethanol (30 mL). The mixture was stirred at room temperature overnight, then filtered and washed with ethanol (20 mL). The filtrate was concentrated, dissolved in ethyl acetate (100 mL) and washed with 1N HCl (1×100 mL) and water (1×100 mL). The organic layer was dried over sodium sulfate, then

concentrated and purified on silica gel column with 10% EtOAc/Hexane to give 5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid ethyl ester Compound **1e** (0.40 g, 16.9%), which was used in the next step without further purification.



Aqueous lithium hydroxide (50 mg in 3 mL of water, 2.1 mmol) was added to a solution of Compound **1e** (0.2 g, 0.42 mmol) in THF (9 mL). Ethanol (1 mL) was added and the mixture was stirred at room temperature for 24 hrs. The reaction mixture was concentrated, diluted with ethyl acetate (100 mL) and washed with 1N HCl (1×100 mL) and water (1×100 mL). The organic layer was dried over sodium sulfate, then filtered and concentrated to give 5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid Compound **1f** (0.18 g, 96%).

A solution of Compound **1f** (0.18 g, 0.40 mmol) in CH_2Cl_2 (2 mL) was treated with thionyl chloride (2 mL). The mixture was heated to reflux for 3 hrs and the solvent was removed in vacuo to obtain 5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carbonyl chloride Compound **1g** (0.18 g, 97.3%).



A solution of Compound **1g** (0.1 g, 0.215 mmol) in CH_2Cl_2 (2 mL) at room temperature was added to a solution of piperidin-1-ylamine Compound **1h** (43 mg, 0.43 mmol) and triethylamine (0.09 mL, 0.65 mmol) in CH_2Cl_2 (8 mL). The resulting

suspension was stirred at room temperature for 2 hrs, then concentrated and purified on silica gel column with 30% EtOAc/Hexane to give Compound **35** (85 mg, 75%). MS 527 (MH^+).

Following the procedure of Example 1, substituting the appropriate starting materials, reagents and solvents, the following compounds were prepared:

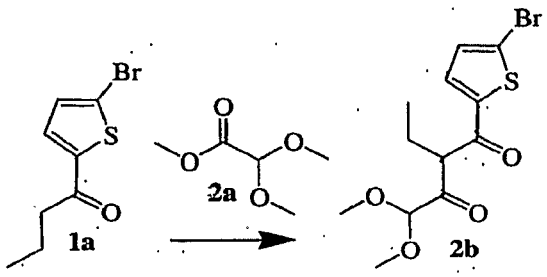
Cpd	Name	MS (MH^+)
1	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide	491
2	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	469
3	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	490
4	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid (4-hydroxy-piperidin-1-yl)-amide	485
5	1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide	462
6	1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	456
7	1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	456
8	1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide	462
9	1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide	457
10	1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	435
11	1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (hexahydro-cyclopenta[c]pyrrol-2-yl)-amide	461
12	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide	496
13	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide	496
14	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	490
15	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	483
16	4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	467
17	4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-pyridin-2-yl-ethyl]-amide	468
18	4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide	473

Cpd	Name	MS (MH$^+$)
19	4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	467
20	4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	446
21	1-(2,4-dichloro-phenyl)-3-(piperidine-1-carbonyl)-5-thiophen-2-yl-1H-pyrazole-4-carbonitrile	431
22	5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	513
23	5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	480
24	5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide	507
25	5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	501
26	5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	501
27	5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-pyridin-2-yl-ethyl]-amide	502
28	1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	453
29	1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	561
30	5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid (2-oxo-piperidin-1-yl)-amide	483
31	1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	474
32	1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	474
33	1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide	474
34	1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide	475
36	1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	582
37	1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide	583
38	1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	582
39	1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide	588
40	5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	548
41	5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide	549

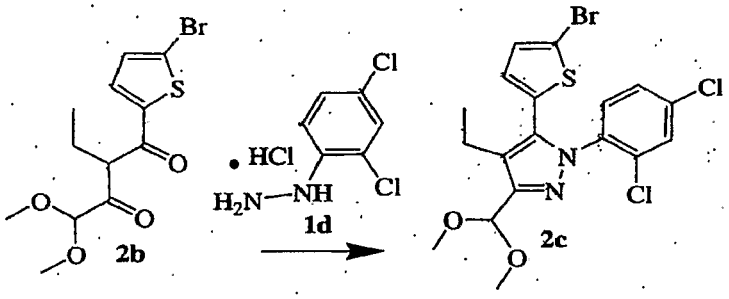
Cpd	Name	MS (MH^+)
42	5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	548
43	5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide	554
44	5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	513
45	[5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazol-3-yl]-piperidin-1-yl-methanone	498
46	5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	534
47	5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide	535
48	5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide	540
49	5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	534
50	[5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazol-3-yl]-(4-hydroxy-piperidin-1-yl)-methanone	528
51	5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid (4-hydroxy-piperidin-1-yl)-amide	543
52	1-{[5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carbonyl]-amino}-1-methyl-piperidinium	542
53	1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide	433
54	1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide	454
55	1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide	454
56	1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid [(1R)-1-pyridin-2-yl-ethyl]-amide	455
57	1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide	460

Example 2

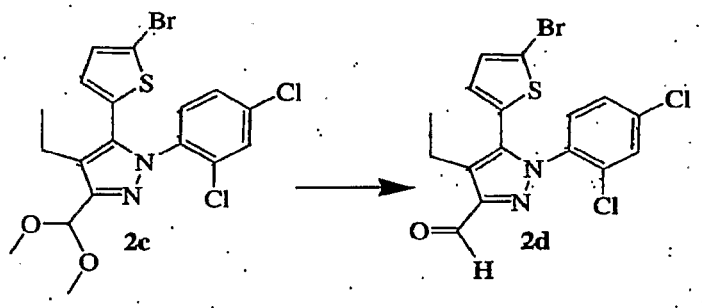
2-[5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazol-3-yl]-ethenesulfonic acid [(1S)-1-phenyl-ethyl]-amide (Cpd **58**).



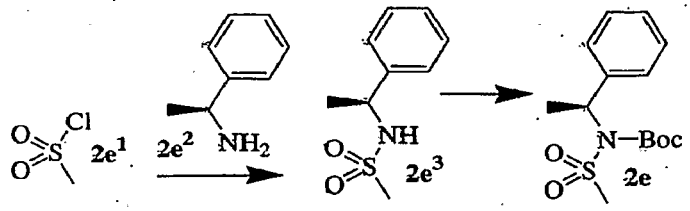
A solution of 1-(5-bromo-thiophen-2-yl)-butan-1-one Compound **1a** (in a suitable solvent) is added to a reagent solution (such as LHMDS in a suitable solvent). The mixture is stirred for a period of time and a solution of dimethoxy-acetic acid methyl ester Compound **2a** (in a suitable solvent) is added. The reaction mixture is stirred for a period of time, then the reaction is quenched. The organic layer is diluted and washed, separated and dried, then filtered and concentrated. The residue is purified to afford 1-(5-bromo-thiophen-2-yl)-2-ethyl-4,4-dimethoxy-butane-1,3-dione Compound **2b**.



Anhydrous (2,4-dichloro-phenyl)-hydrazine hydrochloride Compound **1d** and K_2CO_3 are added to a solution of Compound **2b**. The mixture is stirred for a period of time, then the reaction is quenched. The organic layer is diluted and washed, separated and dried, then filtered and concentrated. The residue is purified to afford Compound 5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-3-dimethoxymethyl-4-ethyl-1H-pyrazole **2c**.

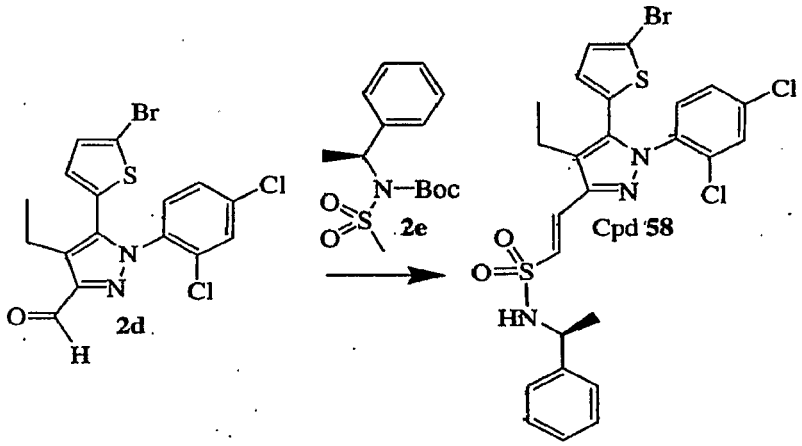


The solution of Compound **2c** is acidified. The reaction mixture is stirred for a period of time, then the reaction is quenched. The organic layer is washed, separated and dried, then filtered and concentrated to afford 5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carbaldehyde Compound **2d**.



A solution of methanesulfonyl chloride Compound **2e**^{1} (in a suitable solvent) is added to a solution of (1*S*)-1-phenyl-ethylamine Compound **2e**^{2} (in a suitable solvent). The mixture is stirred for a period of time, then the reaction is quenched. The organic layer is diluted and washed, separated and dried, then filtered and concentrated to afford N-[(1S)-1-phenyl-ethyl]-methanesulfonamide Compound **2e**^{3}.

$(Boc)_2O$ and DMAP are added to a solution of Compound **2e**^{3} (in a suitable solvent). The reaction mixture is stirred for a period of time, then the reaction is quenched. The organic layer is diluted and washed, separated and dried, then filtered and concentrated. The residue is purified to afford N-(tert-butoxycarbonyl)-N-[(1S)-1-phenyl-ethyl]-methanesulfonamide Compound **2e**.



Adapting a published procedure (Tozer MJ, Woolford AJA and Linney IA, *Synlett,* **1998**, *2*, 186-188), a solution of KOtBu (in a suitable solvent) is added dropwise to a solution of the Compound **2e** (in a suitable solvent). After a period of time, a solution of Compound **2d** (in a suitable solvent) is added. The mixture is reacted for a period of time, then the reaction is quenched. The organic layer is diluted and washed, separated and dried, then filtered and concentrated. The residue is purified to give Compound **58**. MS *m/z* 609 (theoretical MH^+).

Additional compounds may be made according to the synthetic methods of the present invention by one skilled in the art, differing only in possible starting materials, reagents and conditions used in the instant methods.

Biological Examples

The following examples illustrate that the compounds of the present invention are CB receptor modulators useful for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a subject in need thereof.

Example 1

Binding Assay for CB1 or CB2 Agonists or Inverse Agonists

The human CB1 and CB2 receptors were stably expressed in SK-N-MC cells transfected with pcDNA3 CB-1 (human) or pcDNA3 CB-2 (human). The cells were grown in T-180 cell culture flasks under standard cell culture conditions at 37 °C in a 5% CO_2 atmosphere. The cells were harvested by trysinization and homogenized in a homogenization buffer (10 mM Tris, 0.2 mM $MgCl_2$, 5 mM KCl, with protease inhibitors aprotinin, leupeptin, pepstatin A and bacitracin) and centrifuged (2000 g). The supernatant was then centrifuged in 2M sucrose (31,300 g) to produce a semi-purified membrane pellet. The pellet was resuspended in homogenization and stored at -80 °C.

On the day of the assay, the pellet was thawed on ice and diluted in assay buffer (50 mM Tris-HCl, 5 mM $MgCl_2$, 2.5 mM EDTA, 0.5 mg/mL fatty acid free bovine serum albumin, pH 7.5). The diluted membrane pellet was added with buffer, either a test compound or vehicle standard and the radioligand $[H]^{3+}$-CP-55,940 (0.2 nM) to the wells of a 96-well polypropylene plate. Non-specific binding was measured in wells containing WIN 55,212 (10 uM). The plate was covered and incubated for 90 minutes at 30 °C. The contents were then aspirated onto a Packard Unifilter GF/C filter bottom plate prewet with 0.5% polyethyleneimine. The wells of the polypropylene plate were rinsed and aspirated seven times with a 0.9% saline-0.5% Tween 20 solution. The Unifilter plate was dried, scintillation cocktail was added to each well and the counts representing binding were quantitated in a TopCount scintillation counter.

CB1 and CB2 Receptor Binding Results

For compounds tested, an IC_{50} binding value was obtained from percent inhibition studies in which various test concentrations were used. The binding value was calculated by linear regression.

For compounds without an IC_{50} binding value, the percent inhibition (%) was obtained at a test concentration of 0.2 μM.

Table 1

Cannabinoid CB1 Receptor Binding

Cpd	Binding	Cpd	Binding	Cpd	Binding
1	0.038	20	37%	39	0.018
2	0.04	21	12%	40	78%
3	0.035	22	0.037	41	0.015
4	27%	23	0.071	42	0.011
5	43%	24	0.015	43	0.008
6	57%	25	0.016	44	74%
7	28%	26	0.11	45	33%
8	34%	27	69%	46	52%
9	25%	28	69%	47	56%
10	37%	29	0.017	48	60%
11	53%	30	17%	49	76%
12	0.015	31	64%	50	28%
13	0.074	32	0.046	51	63%
14	0.027	33	73%	52	51%
15	0.012	34	61%	53	40%
16	61%	35	0.013	54	0.14
17	25%	36	0.017	55	58%
18	66%	37	0.031	56	41%
19	45%	38	0.023	57	46%

Table 2

Cannabinoid CB2 Receptor Binding

Cpd	Binding	Cpd	Binding	Cpd	Binding
4	11%	21	3%	42	38%
5	15%	22	42%	43	39%
6	8%	23	22%	44	53%
7	0%	24	13%	45	12%
8	1%	25	13%	46	47%
9	8%	26	16%	47	46%
10	6%	27	12%	48	49%

Cpd	Binding	Cpd	Binding	Cpd	Binding
11	0%	28	20%	49	63%
12	40%	29	55%	50	17%
13	37%	30	15%	51	13%
14	40%	31	39%	52	0%
15	29%	32	55%	53	21%
16	17%	33	41%	54	52%
17	14%	34	34%	55	30%
18	21%	35	29%	56	26%
19	24%	40	52%	57	28%
20	9%	41	45%		

Example 2

Functional Cell-Based Assay for CB1 or CB2 Agonist and Inverse Agonist Effects on Intra-Cellular Adenylate Cyclase Activity

The CB1 and CB2 receptors are G-protein coupled receptors (GPCR), which influence cell function via the Gi-protein. These receptors modulate the activity of intracellular adenylate cyclase, which in turn produces the intracellular signal messenger cyclic-AMP (cAMP).

At baseline, or during non-ligand bound conditions, these receptors are constitutively active and tonically suppress adenylate cyclase activity. The binding of an agonist causes further receptor activation and produces additional suppression of adenylate cyclase activity. The binding of an inverse agonist inhibits the constitutive activity of the receptors and results in an increase in adenylate cyclase activity.

By monitoring intracellular adenylate cyclase activity, the ability of compounds to act as agonists or inverse agonists can be determined.

Assay

Test compounds are evaluated in SK-N-MC cells which, using standard transfection procedures, are stably transfected with human cDNA for pcDNA3–CRE β-gal and pcDNA3 CB1 receptor (human) or pcDNA3 CB2 receptor (human). By expressing CRE β-gal, the cells produce β-galactosidase in response to CRE promoter activation by cAMP. Cells expressing CRE β-gal and either the human CB1 or CB2 receptor will produce less β-galactosidase when treated with a CB1/CB2 agonist and will produce more β-galactosidase when treated with a CB1/CB2 inverse agonist.

Cell Growth

The cells are grown in 96-well plates under standard cell culture conditions at 37 °C in a 5% CO_2 atmosphere. After 3 days, the media is removed and a test compound in media (wherein the media is supplemented with 2 mM L-glutamine, 1M sodium pyruvate, 0.1% low fatty acid FBS (fetal bovine serum) and antibiotics) is added to the cell. The plates are incubated for 30 minutes at 37 °C and the plate cells are then treated with forskolin over a 4-6 hour period, then washed and lysed. The β-galactosidase activity is quantitated using commercially available kit reagents (Promega Corp. Madison, WI) and a Vmax Plate Reader (Molecular Devices, Inc).

CB1 Receptor Mediated Change in CRE β-gal Expression

For cells expressing CRE β-gal and the CB1 receptor, CB1 agonists reduce β-galactosidase activity in a dose-dependent manner and CB1 inverse agonists increase β-galactosidase activity in a dose-dependent manner.

The change in β-galactosidase activity is determined by setting a vehicle treated cell's activity value at 100% and expressing the β-galactosidase activity measured in a corresponding compound treated cell as a percent of the vehicle treated cell activity.

CB2 Receptor Mediated Change in CRE β-gal Expression

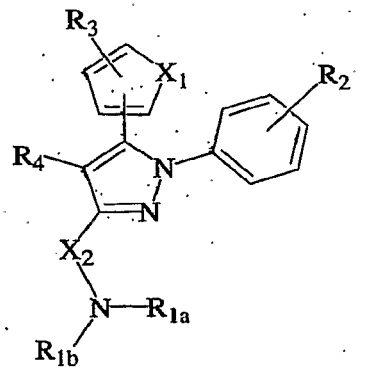
For cells expressing CRE β-gal and the CB2 receptor, CB2 agonists reduce β-galactosidase activity in a dose-dependent manner and CB2 inverse agonists increase β-galactosidase activity in a dose-dependent manner.

The change in β-galactosidase activity is determined by setting a vehicle treated cell's activity value at 100% and expressing the β-galactosidase activity measured in a corresponding compound treated cell as a percent of the vehicle treated cell activity.

It is to be understood that the preceding description of the invention and various examples thereof have emphasized certain aspects. Numerous other equivalents not specifically elaborated on or discussed may nevertheless fall within the spirit and scope of the present invention or the following claims and are intended to be included.

What is claimed is:

1. A compound having a structure according to formula (I):



or a form thereof, wherein

X_1 is N, O or S;

X_2 is carbonyl, alkenyl-carbonyl or alkenyl-sulfonyl;

R_{1a} is absent or hydrogen,

wherein R_{1a} is absent when R_{1a} and R_{1b} are taken together with the formula (I) nitrogen atom to form a heterocyclyl ring optionally substituted with one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, oxo, amino or aminoalkyl,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl;

R_{1b} is selected from C_{3-12} cycloalkyl, heterocyclyl, aryl, heteroaryl or alkyl substituted with C_{3-12} cycloalkyl, heterocyclyl, aryl or heteroaryl, wherein each of C_{3-12} cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, oxo, amino or aminoalkyl,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl, and

wherein heterocyclyl optionally has one nitrogen ring atom and said atom is attached to the formula (I) nitrogen atom, and wherein said atom is

optionally further substituted with alkyl to form a quaternary ammonium salt;

R_2 is one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, amino, aminoalkyl, aminosulfonylalkyl or sulfonylaminoalkyl,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl;

R_3 is one or two substituents selected from hydrogen, alkyl, alkoxy, cyano or halogen,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl; and,

R_4 is one, two or three substituents selected from alkyl, alkoxy, cyano or halogen,

wherein the alkyl and alkoxy substituents are optionally substituted with one, two or three substituents selected from alkoxy, cyano, halogen, hydroxy, amino or aminoalkyl.

2. The compound of claim 1, wherein X_1 is O or S.

3. The compound of claim 1, wherein X_2 is carbonyl or alkenyl-sulfonyl.

4. The compound of claim 1, wherein R_{1a} is hydrogen.

5. The compound of claim 1, wherein R_{1a} is absent when R_{1a} and R_{1b} are taken together with the formula (I) nitrogen atom to form a heterocyclyl ring optionally substituted with one or two substituents selected from alkyl, hydroxy or oxo.

6. The compound of claim 1, wherein R_{1b} is selected from heterocyclyl or alkyl substituted with C_{3-12} cycloalkyl, aryl or heteroaryl, wherein each of C_{3-12} cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, oxo, amino or aminoalkyl, wherein heterocyclyl optionally has one nitrogen ring atom and said atom is attached to the formula (I) nitrogen atom,

and wherein said atom is optionally further substituted with alkyl to form a quaternary ammonium salt.

7. The compound of claim 1, wherein R_2 is one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, amino, aminoalkyl, aminosulfonylalkyl or sulfonylaminoalkyl.

8. The compound of claim 1, wherein R_2 is one, two, three or four halogen substituents.

9. The compound of claim 1, wherein R_3 is one or two substituents selected from hydrogen, alkyl, alkoxy, cyano or halogen.

10. The compound of claim 1, wherein R_3 is one or two substituents selected from hydrogen, alkyl or halogen.

11. The compound of claim 1, wherein R_4 is one, two or three substituents selected from alkyl, alkoxy, cyano or halogen.

12. The compound of claim 1, wherein R_4 is one, two or three substituents selected from alkyl or cyano.

13. The compound of claim 1, wherein

X_1 is O or S;

X_2 is carbonyl or alkenyl-sulfonyl;

R_{1a} is absent or hydrogen,

wherein R_{1a} is absent when R_{1a} and R_{1b} are taken together with the formula (I) nitrogen atom to form a heterocyclyl ring optionally substituted with one or two substituents selected from alkyl, hydroxy or oxo;

R_{1b} is selected from heterocyclyl or alkyl substituted with C_{3-12} cycloalkyl, aryl or heteroaryl, wherein each of C_{3-12} cycloalkyl, heterocyclyl, aryl or heteroaryl is optionally substituted with one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, oxo, amino or aminoalkyl,

wherein heterocyclyl optionally has one nitrogen ring atom and said atom is attached to the formula (I) nitrogen atom, and wherein said atom is

optionally further substituted with alkyl to form a quaternary ammonium salt;

R_2 is one, two, three or four substituents selected from alkyl, alkoxy, cyano, halogen, hydroxy, amino, aminoalkyl, aminosulfonylalkyl or sulfonylaminoalkyl;

R_3 is one or two substituents selected from hydrogen, alkyl, alkoxy, cyano or halogen; and,

R_4 is one, two or three substituents selected from alkyl, alkoxy, cyano or halogen.

14. The compound of claim 1, wherein the compound is an isolated form thereof.

15. The compound of claim 14, wherein the compound is a cannabinoid receptor modulator, wherein the cannabinoid receptor is a CB1 or CB2 receptor, and wherein the modulator compound is an agonist, antagonist or inverse-agonist of the receptor.

16. A composition comprising an effective amount of a compound of claim 15 and a pharmaceutically acceptable carrier.

17. The composition of claim 16, wherein the effective amount is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.

18. A process for preparing a composition comprising the step of admixing a compound of claim 15 and a pharmaceutically acceptable carrier.

19. A medicament comprising an effective amount of a compound of claim 15.

20. A method for using the compound of claim 15 for modulating cannabinoid receptor activity comprising contacting the receptor with the compound.

21. A method for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of the compound of claim 15.

22. The method of claim 21, wherein the syndrome, disorder or disease is related to appetite, metabolism, diabetes, glaucoma-associated intraocular pressure, social

and mood disorders, seizures, substance abuse, learning, cognition or memory, organ contraction or muscle spasm, bowel disorders, respiratory disorders, locomotor activity or movement disorders, immune and inflammation disorders, unregulated cell growth, pain management or neuroprotection.

23. The method of claim 21, wherein the effective amount of the compound is from about 0.001 mg/kg/day to about 300 mg/kg/day.

24. The method of claim 21, further comprising treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated appetite related, obesity related or metabolism related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of the compound, wherein the compound is an inverse-agonist of the receptor.

25. The method of claim 24, wherein the effective amount of the compound is from about 0.001 mg/kg/day to about 300 mg/kg/day.

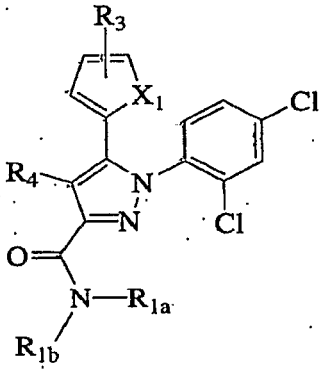
26. The method of claim 24, further comprising the step of administering to the subject a combination product comprising an effective amount of the compound and a therapeutic agent, wherein the therapeutic agent is an anticonvulsant or a contraceptive agent.

27. The method of claim 26, wherein the anticonvulsant is topiramate, analogs of topiramate, carbamazepine, valproic acid, lamotrigine, gabapentin, phenytoin and the like and mixtures or pharmaceutically acceptable salts thereof.

28. The method of claim 26, wherein the contraceptive agent is a progestin-only contraceptive, a contraceptive having a progestin component and an estrogen component, or an oral contraceptive optionally having a folic acid component.

29. A method of contraception in a subject comprising the step of administering to the subject a composition, wherein the composition comprises a contraceptive and the compound of claim 14, wherein the composition reduces the urge to smoke in the subject or assists the subject in losing weight or both, and wherein the compound is a CB1 receptor inverse-agonist or antagonist.

30. A compound of formula (Ia):



or a form thereof, wherein

X_1 is O or S;

R_{1a} is absent or hydrogen,

wherein R_{1a} is absent when R_{1a} and R_{1b} are taken together with the formula (I) nitrogen atom to form a heterocyclyl ring optionally substituted with one or two substituents selected from alkyl, hydroxy or oxo;

R_{1b} is selected from heterocyclyl or alkyl substituted with C_{3-12} cycloalkyl, aryl or heteroaryl, wherein heterocyclyl is optionally substituted with one substituent selected from alkyl, hydroxy or oxo,

wherein heterocyclyl optionally has one nitrogen ring atom and said atom is attached to the formula (I) nitrogen atom, and wherein said atom is optionally further substituted with alkyl to form a quaternary ammonium salt;

R_3 is one substituent selected from hydrogen, alkyl or halogen; and,

R_4 is one substituent selected from alkyl or cyano.

31. The compound of claim 30, wherein the compound is an isolated form thereof.

32. The compound of claim 31, wherein the compound is a cannabinoid receptor modulator, wherein the cannabinoid receptor is a CB1 or CB2 receptor, and wherein the modulator compound is an agonist, antagonist or inverse-agonist of the receptor.

33. A composition comprising an effective amount of a compound of claim 32 and a pharmaceutically acceptable carrier.

34. The composition of claim 33, wherein the effective amount is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.

35. A process for preparing a composition comprising the step of admixing a compound of claim 32 and a pharmaceutically acceptable carrier.

36. A medicament comprising an effective amount of a compound of claim 32.

37. A method for using the compound of claim 32 for modulating cannabinoid receptor activity comprising contacting the receptor with the compound.

38. A method for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of the compound of claim 32.

39. The method of claim 38, wherein the syndrome, disorder or disease is related to appetite, metabolism, diabetes, glaucoma-associated intraocular pressure, social and mood disorders, seizures, substance abuse, learning, cognition or memory, organ contraction or muscle spasm, bowel disorders, respiratory disorders, locomotor activity or movement disorders, immune and inflammation disorders, unregulated cell growth, pain management or neuroprotection.

40. The method of claim 38, wherein the effective amount of the compound is from about 0.001 mg/kg/day to about 300 mg/kg/day.

41. The method of claim 38, further comprising treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated appetite related, obesity related or metabolism related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of the compound, wherein the compound is an inverse-agonist of the receptor.

42. The method of claim 41, wherein the effective amount of the compound is from about 0.001 mg/kg/day to about 300 mg/kg/day.

43. The method of claim 38, further comprising the step of administering to the subject a combination product comprising an effective amount of the compound

and a therapeutic agent, wherein the therapeutic agent is an anticonvulsant or a contraceptive agent.

44. The method of claim 43, wherein the anticonvulsant is topiramate, analogs of topiramate, carbamazepine, valproic acid, lamotrigine, gabapentin, phenytoin and the like and mixtures or pharmaceutically acceptable salts thereof.

45. The method of claim 43, wherein the contraceptive agent is a progestin-only contraceptive, a contraceptive having a progestin component and an estrogen component, or an oral contraceptive optionally having a folic acid component.

46. A method of contraception in a subject comprising the step of administering to the subject a composition, wherein the composition comprises a contraceptive and the compound of claim 32, wherein the composition reduces the urge to smoke in the subject or assists the subject in losing weight or both, and wherein the compound is a CB1 receptor inverse-agonist or antagonist.

47. A compound or a form thereof selected from the group consisting of

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-4-methyl-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid (hexahydro-cyclopenta[c]pyrrol-2-yl)-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

4-cyano-1-(2,4-dichloro-phenyl)-5-thiophen-2-yl-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-cyclohexyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

5-(5-chloro-thiophen-2-yl)-4-cyano-1-(2,4-dichloro-phenyl)-1H-pyrazole-3-carboxylic acid [(1R)-1-pyridin-2-yl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-fluoro-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

1-(2,4-dichloro-phenyl)-5-(5-iodo-thiophen-2-yl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-pyridin-2-yl-ethyl]-amide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1S)-1-cyclohexyl-ethyl]-amide,

5-(4-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide,

5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carboxylic acid (4-hydroxy-piperidin-1-yl)-amide,

1-{[5-(5-bromo-thiophen-2-yl)-1-(2,4-dichloro-phenyl)-4-ethyl-1H-pyrazole-3-carbonyl]-amino}-1-methyl-piperidinium,

1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid [(1S)-1-phenyl-ethyl]-amide, and

1-(2,4-dichloro-phenyl)-4-methyl-5-(5-methyl-furan-2-yl)-1H-pyrazole-3-carboxylic acid [(1R)-1-phenyl-ethyl]-amide.

48. The compound of claim 47, wherein the compound is an isolated form thereof.

49. The compound of claim 48, wherein the compound is a cannabinoid receptor modulator, wherein the cannabinoid receptor is a CB1 or CB2 receptor, and wherein the modulator compound is an agonist, antagonist or inverse-agonist of the receptor.

50. A composition comprising an effective amount of a compound of claim 49 and a pharmaceutically acceptable carrier.

51. The composition of claim 50, wherein the effective amount is in a range of from about 0.001 mg/kg to about 300 mg/kg of body weight per day.

52. A process for preparing a composition comprising the step of admixing a compound of claim 49 and a pharmaceutically acceptable carrier.

53. A medicament comprising an effective amount of a compound of claim 49.

54. A method for using the compound of claim 49 for modulating cannabinoid receptor activity comprising contacting the receptor with the compound.

55. A method for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a subject in need thereof comprising

the step of administering to the subject an effective amount of the compound of claim 49.

56. The method of claim 55, wherein the syndrome, disorder or disease is related to appetite, metabolism, diabetes, glaucoma-associated intraocular pressure, social and mood disorders, seizures, substance abuse, learning, cognition or memory, organ contraction or muscle spasm, bowel disorders, respiratory disorders, locomotor activity or movement disorders, immune and inflammation disorders, unregulated cell growth, pain management or neuroprotection.

57. The method of claim 55, wherein the effective amount of the compound is from about 0.001 mg/kg/day to about 300 mg/kg/day.

58. The method of claim 55, further comprising treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated appetite related, obesity related or metabolism related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of the compound, wherein the compound is an inverse-agonist of the receptor.

59. The method of claim 58, wherein the effective amount of the compound is from about 0.001 mg/kg/day to about 300 mg/kg/day.

60. The method of claim 55, further comprising the step of administering to the subject a combination product comprising an effective amount of the compound and a therapeutic agent, wherein the therapeutic agent is an anticonvulsant or a contraceptive agent.

61. The method of claim 60, wherein the anticonvulsant is topiramate, analogs of topiramate, carbamazepine, valproic acid, lamotrigine, gabapentin, phenytoin and the like and mixtures or pharmaceutically acceptable salts thereof.

62. The method of claim 60, wherein the contraceptive agent is a progestin-only contraceptive, a contraceptive having a progestin component and an estrogen component, or an oral contraceptive optionally having a folic acid component.

63. A method of contraception in a subject comprising the step of administering to the subject a composition, wherein the composition comprises a contraceptive

and the compound of claim 49, wherein the composition reduces the urge to smoke in the subject or assists the subject in losing weight or both, and wherein the compound is a CB1 receptor inverse-agonist or antagonist.