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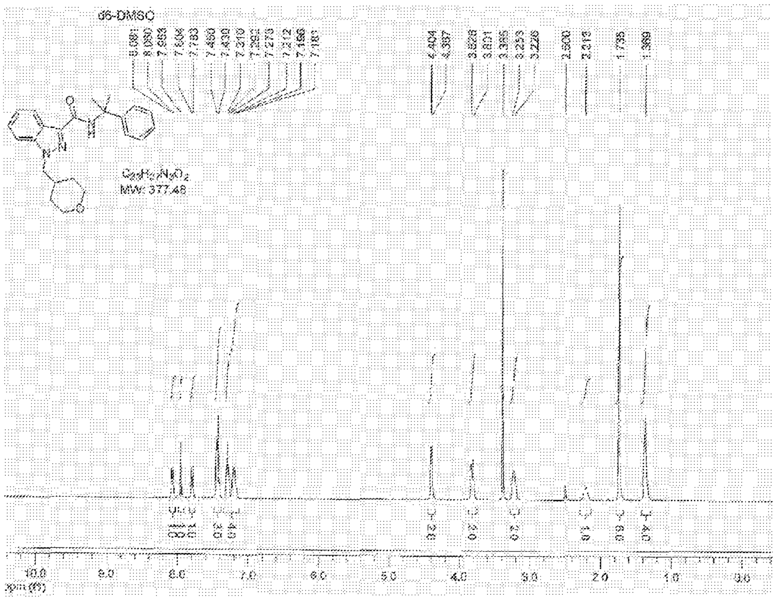


Fig. 1

(57) **Abstract**: The present invention relates generally to cannabinoid compounds, more particularly indole and indazole compounds of formula I and Ia and pharmaceutical compositions comprising the compounds. The compounds are useful treating pain, treating nausea and/or emesis, stimulating appetite, inducing a euphoric effect, inducing relaxation, and inducing a positive mood change, in particular for treating pain, treating nausea and/or emesis, and stimulating appetite.

CANNABINOID COMPOUNDS

1. FIELD OF THE INVENTION

The present invention relates generally to cannabinoid compounds and compositions, more particularly new indole and indazole cannabinoids and compositions, and applications of these.

2. BACKGROUND OF THE INVENTION

Cannabinoids are a class of diverse chemical compounds that activate cannabinoid receptors. The broader definition of the term "cannabinoids" refers to a group of compounds that are structurally related to tetrahydrocannabinol (THC) or that bind to cannabinoid receptors. Such compounds include the endocannabinoids (produced naturally in the body by humans and animals), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (produced chemically by humans). The most notable cannabinoid is delta-9 THC, the primary psychoactive compound of cannabis. However, there are numerous other known synthetic and natural cannabinoids.

Delta-9 THC, the principle active component of cannabis, is a member of a large family of cannabinoid compounds that mediate physiological and psychotropic effects including immunosuppression, analgesia, inflammation, emesis, and intraocular pressure. Cannabinoids work through selective binding to G-protein coupled cannabinoid receptors. Two types of cannabinoid receptors have been cloned: CB_1 and CB_2. The CB_1 receptor is found mainly on cells of the central nervous system, while the CB_2 receptor is found mainly on cells of the peripheral nervous system including cells comprising the immune system, such as lymphoid cells.

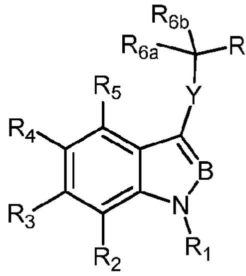
Cannabinoid compounds that bind to CB_1 and/or CB_2 receptors, such as delta-9 THC, are known to have gastrointestinal, cardiovascular, and/or central nervous system activity. Such compounds may, therefore, offer therapeutic approaches to a variety of diseases or conditions.

There is a need to provide alternatives to known cannabinoid compounds. It is an object of the invention to at least go some way towards meeting this need, and/or to at least provide the public with a useful choice.

In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

3. SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a compound of formula I,



I

wherein

Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, (C=S)NH, SCH_2, OCH_2, CH_2SO_2, OSO_2, $NHSO_2$,O(C=O), O(C=S), S(C=O), CH_2(C=O), CH_2(C=S), CH_2(C=SO_2), O(C=SO_2), NH(C=SO_2), NH(C=O), or NH(C=S);

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted;

R_2-R_5 are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

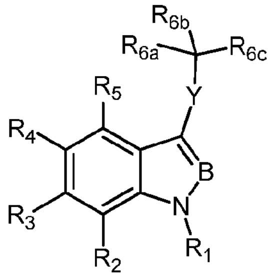
R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or a 3 to 7 membered heterocyclyl ring; and

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, heteroaryl, or cyano, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl which may be optionally substituted; or

a pharmaceutically acceptable salt or prodrug thereof.

In a second aspect, the present invention provides a compound of formula I,



I

wherein

Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, (C=S)NH, SCH_2, OCH_2, CH_2SO_2, OSO_2, $NHSO_2$,O(C=O), O(C=S), S(C=O), CH_2(C=O), CH_2(C=S), CH_2(C=SO_2), O(C=SO_2), NH(C=SO_2), NH(C=O), or NH(C=S);

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted;

R_2-R_5 are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

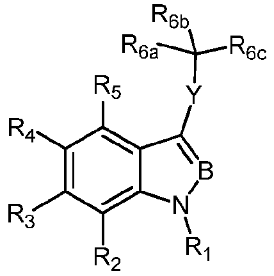
R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring; and

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl which may be optionally substituted; or

a pharmaceutically acceptable salt or prodrug thereof.

In a third aspect, the invention provides the present invention provides a compound of formula I,



I

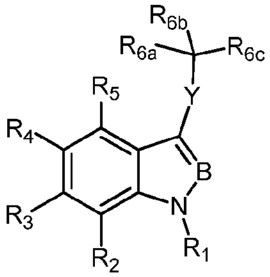
wherein

R_{6a} and R_{6b} together form 3 to 7 membered heterocycle; and

Y, B, R_1, R_2-R_5, and R_{6c} are as defined in first aspect above;

a pharmaceutically acceptable salt or prodrug thereof.

In a fourth aspect, the invention provides the present invention provides a compound of formula I,



I

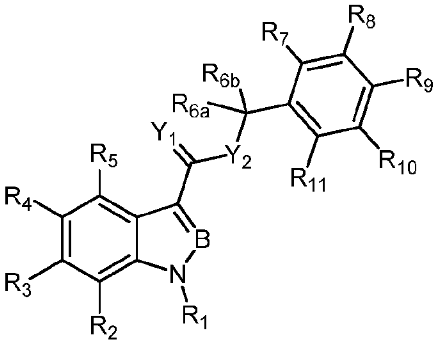
wherein

R_{6c} is cyano; and

Y, B, R_1, R_2-R_5, R_{6a} and R_{6b} are as defined in the first aspect above;

a pharmaceutically acceptable salt or prodrug thereof.

In a fifth aspect, the invention the present invention provides a compound of formula Ia,



Ia

wherein

Y_1 is selected from O, S, or SO_2;

Y_2 is selected from CH_2, O, or NH;

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted;

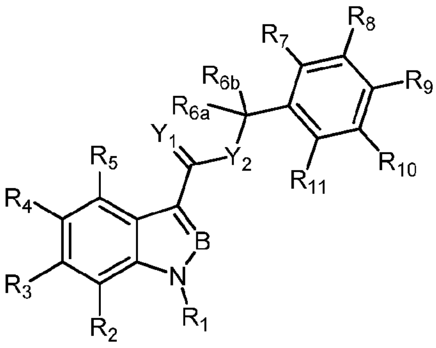
R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or 3 to 7 membered heterocyclyl ring; and

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted; or

a pharmaceutically acceptable salt or prodrug thereof.

In a sixth aspect, the present invention provides a compound of formula Ia,



Ia

wherein

Y_1 is selected from O, S, or SO_2;

Y_2 is selected from CH_2, O, or NH;

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted;

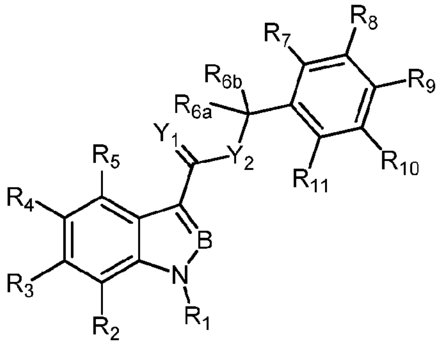
R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring; and

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted; or

a pharmaceutically acceptable salt or prodrug thereof.

In seventh aspect, the invention provides the present invention provides a compound of formula Ia,



Ia

wherein

R_{6a} and R_{6b} together form 3 to 7 membered heterocycle; and

Y_1, Y_2, B, R_1, R_2-R_5 and R_7-R_{11} are as defined in fifth aspect above;

a pharmaceutically acceptable salt or prodrug thereof.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

In another aspect, the invention relates to a compound of the invention for use in treating pain in a subject.

In another aspect, the invention related to a compound of the invention for use in treating nausea and/or emesis in a subject.

In another aspect, the invention relates to a compound of the invention for use in stimulating appetite in a subject.

In another aspect, the invention relates to a compound of the invention for use in inducing a euphoric effect in a subject.

In another aspect, the invention relates to a compound of the invention for use in relaxing a subject.

In another aspect, the invention relates to a compound of the invention for use in inducing a positive mood change in a subject.

To those skilled in the art to which the invention relates, many changes in construction and widely differing embodiments and applications of the invention will suggest themselves without departing from the scope of the invention as defined in the appended claims. The disclosures and the descriptions herein are purely illustrative and are not intended to be in any sense limiting

Other features of the invention may become apparent from the following description which is given by way of example only.

4. BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described with reference to the Figures in which:

Figure 1 shows a 1H NMR scan for the compound SGT-42.

Figure 2 shows a 13C NMR scan for the compound SGT-42.

5. DETAILED DESCRIPTION OF THE INVENTION

5.1 Definitions

As used herein “(s)” following a noun means the plural and/or singular forms of the noun.

As used herein the term “and/or” means “and” or “or” or both.

As used herein, the term “comprising” as used in this specification means “consisting at least in part of”. When interpreting each statement in this specification that includes the term “comprising”, features other than that or those prefaced by the term may also be present. Related terms such as “comprise” and “comprises” are to be interpreted in the same manner.

It is intended that reference to a range of numbers disclosed herein (for example, 1 to 10) also incorporates reference to all rational numbers within that range (for example, 1, 1.1, 2, 3, 3.9, 4, 5, 6, 6.5, 7, 8, 9 and 10) and also any range of rational numbers within that range (for example, 2 to 8, 1.5 to 5.5 and 3.1 to 4.7) and, therefore, all sub-ranges of all ranges expressly disclosed herein are hereby expressly disclosed. These are only examples of what is specifically intended and all possible combinations of numerical values between the lowest value and the highest value enumerated are to be considered to be expressly stated in this application in a similar manner.

The term “therapeutically effective amount”, as used herein, means the amount of an active compound, or a material, composition, composition, or dosage form comprising an active compound, which is effective for producing some desired therapeutic or prophylactic effect, commensurate with a reasonable benefit/risk ratio. Therapeutically effective amounts can be determined using routine optimisation techniques well known in the art.

The term “pharmaceutically acceptable” as used herein in conjunction with the terms "salt", "prodrug", or "carrier" refers to compounds of the invention, ingredients, materials and the like, which are within the scope of sound medical judgment, suitable for use in contact with the tissues of a human without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier must also be “acceptable” in the sense of being compatible with the other ingredients of the composition.

The term “treatment”, and related terms, such as “treating” and “treat” as used herein, in the context of treating a condition, relates generally to treatment of a human, in which some desired therapeutic effect is achieved. The therapeutic effect may, for example, be the inhibition of progress of the condition, including a reduction in the rate of progress; a halt in the rate of progress of the condition; amelioration of the condition; and cure of the condition.

Treatment as a prophylactic measure (i.e., prophylaxis) is also included. Treatment also includes combination treatments and therapies, in which two or more treatments or therapies are used, for example, sequentially or simultaneously, in combination. For example, a therapeutically effective amount of a compound of the invention could be combined with or used in conjunction with a known cannabinoid compound.

The term "cannabinomimetic" as used herein means having similar effects to the effects of cannabis when administered to a subject.

The term "alkyl" means a saturated hydrocarbon radical containing normal, secondary, or tertiary carbon atoms. Examples of suitable alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl ($-CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl ($-CH(CH_2CH_3)(CH_2CH_2CH_3)$)), 2-methyl-2-pentyl ($-C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl ($-CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl ($-CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl ($-C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl ($-CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl ($-C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl ($-CH(CH_3)C(CH_3)_3$, and octyl ($-(CH_2)_7CH_3$).

The term "alkenyl" means a hydrocarbon radical containing normal, secondary, tertiary or cyclic carbon atoms with at least one double bond. Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2CH_2CH_2CH_2CH=CH_2$).

The term "alkynyl" means a hydrocarbon radical containing normal, secondary, tertiary or cyclic carbon atoms with at least one triple bond. Examples of suitable alkynyl groups include, but are not limited to, acetylenic ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), and the like.

The term “cycloalkyl” means a hydrocarbon radical containing a saturated ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system, or spiro-fused rings.

The terms “cycloalkenyl” and “cycloalkynyl” have analogous meanings.

The term “aryl” means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

The term “alkoxy” means a group having the formula –O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. Examples of suitable alkoxy groups include, but are not limited to, methoxy ($-O-CH_3$ or –OMe), ethoxy ($-OCH_2CH_3$ or -OEt), t-butoxy ($-O-C(CH_3)_3$ or –OtBu) and the like.

The term “halo” as used herein means iodo, bromo, chloro, or fluoro.

The term “haloalkyl” means an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halo group. Examples of suitable haloalkyl groups include, but are not limited to, $-(CH_2)_nF$, $-CF_3$, $-CHF_2$, $-CFH_2$, $-CH_2CF_3$, and the like.

The terms “haloalkenyl” and “haloalkynyl” have analogous meanings.

The term “optionally substituted” in reference to a particular moiety of the compound of the invention (e.g., an optionally substituted aryl group) refers to a moiety having 0, 1, 2, or more substituents.

The term "substituted" in reference to alkyl, alkenyl, alkynyl, halogen, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl means alkyl, alkenyl, alkynyl, halogen, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, -NHS$(=O)_2$R, -C(=O)R, -C(=O)NRR, -S$(=O)_2$OH, -S$(=O)_2$R, -OS$(=O)_2$OR, -S$(=O)_2$NR, -S(=O)R, -OP(=O)$(OR)_2$, -P(=O)$(OR)_2$, -P(=O)$(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR, where each X is independently halo; and each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, a C_3-C_{12} heterocycle, or a protecting group (PG). When the number of carbon atoms is designated for a substituted group, the number of carbon atoms refers to the group, not the substituent (unless otherwise indicated). For example, a C_{1-4} substituted alkyl refers to a C_{1-4} alkyl, which can be substituted with groups having more than the, e.g., 4 carbon atoms.

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the compound of the invention, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalysed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analogue or latent form of a therapeutically active compound.

One skilled in the art will recognise that substituents and other moieties of the compounds of Formula I should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of the invention which have such stability are contemplated as falling within the scope of the present invention.

The term "heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., $-OCH_3$, etc.), an amine (e.g., $-NHCH_3$, $-N(CH_3)_2$, etc.), or a thioalkyl group (e.g., $-SCH_3$). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., $-CH_2CH_2-O-CH_3$, etc.), an alkyl amine (e.g., $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, etc.), or a thioalkyl ether (e.g.,$-CH_2-S-CH_3$). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., $-CH_2CH_2-OH$), an aminoalkyl group (e.g., $-CH_2NH_2$), or an alkyl thiol group (e.g., $-CH_2CH_2-SH$). A heteroalkyl group can have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C_1-C_6 heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

The terms “heterocycle” or “heterocyclyl” as used herein include by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs” (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. The terms “heterocycle” and “heterocyclyl” include saturated rings (i.e., heterocycloalkyls), partially unsaturated rings, and aromatic rings (*i.e.*, heteroaromatic rings). The terms “heterocycle” and “heterocyclyl” also include substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. Examples of substituted heterocycles include, but are not limited to, 4,4-difluoro-1-piperidinyl and N-methyl-2-piperidinyl.

The term “heterocycle” or “heterocyclyl” employed alone or in combination with other terms means, unless otherwise stated, a saturated or unsaturated non-aromatic monocyclic heterocyclyl ring or a bicyclic heterocyclyl ring. Monocyclic heterocyclyl rings include monovalent 3-, 4-, 5-, 6-, or 7-membered rings containing one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, and sulfur in the ring. Monocyclic heterocyclyl groups are connected to the parent molecular moiety through any available carbon atom or nitrogen atom within the ring. Examples of monocyclic heterocyclyl groups include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiopyranyl, and trithianyl. Bicyclic heterocyclyl rings include monovalent monocyclic heterocyclyl rings fused to phenyl rings, cycloalkyl rings, or other monocyclic heterocyclyl rings. Bicyclic heterocyclyl groups are connected to the parent molecular moiety through any available carbon atom or nitrogen atom within the rings. Examples of bicyclic heterocyclyl groups include, but are not limited to, 1,3-benzodioxolyl, 1,3-benzodithiolyl, 2,3-dihydro-1,4-benzodioxinyl, 2,3-dihydro-1-benzofuranyl, 2,3-dihydro-1-benzothienyl, 2,3-dihydro-1H-indolyl, and 1,2,3,4-tetrahydroquinolinyl. In some embodiments the heterocyclyl is monocyclic.

"Heteroaryl" refers to an aromatic heterocyclyl. Non-limiting examples of suitable heteroatoms which can be included in the aromatic ring include oxygen, sulphur, and nitrogen. Non-limiting examples of heteroaryl rings include pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

The term "halogenating agent" includes phosphorous oxychloride, thionyl chloride, oxalyl chloride, phosphorous trichloride, phosphorous pentachloride, and diphosgene.

The term "halogenated solvent" includes chloroform, dichloromethane, and carbon tetrachloride.

The term “chiral” refers to molecules which have the property of non-superimposability of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

The term “stereoisomers” refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

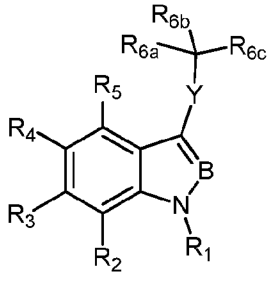
“Diastereomer” refers to a stereoisomer with two or more centres of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

“Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

5.2 The compounds of the invention

The invention provides cannabinoid compounds that have a range of therapeutic activities including analgesic, anti-inflammatory, and anti-emetic. The compounds of the invention also have psychotropic effects so can be used as relaxants to induce positive mood change.

In one aspect, the present invention provides a compound of formula I,



I

wherein

Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, (C=S)NH, SCH_2, OCH_2, CH_2SO_2, OSO_2, $NHSO_2$,O(C=O), O(C=S), S(C=O), CH_2(C=O), CH_2(C=S), CH_2(C=SO_2), O(C=SO_2), NH(C=SO_2), NH(C=O), or NH(C=S);

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted;

R_2-R_5 are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

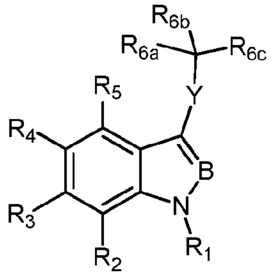
R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring; and

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl which may be optionally substituted; or

a pharmaceutically acceptable salt or prodrug thereof.

In another aspect, the present invention provides a compound of formula I,



I

wherein

Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH,

(C=S)NH, SCH_2, OCH_2, CH_2SO_2, OSO_2, $NHSO_2$,O(C=O), O(C=S), S(C=O), CH_2(C=O), CH_2(C=S), CH_2(C=SO_2), O(C=SO_2), NH(C=SO_2), NH(C=O), or NH(C=S);

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -Br, -F, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, -NHS$(=O)_2$R, -C(=O)R, -C(=O)NRR, -S$(=O)_2$OH, -S$(=O)_2$R, -OS$(=O)_2$OR, -S$(=O)_2$NR, -S(=O)R, -OP(=O)$(OR)_2$, -P(=O)$(OR)_2$, -P(=O)$(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_2-R_5 are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, -NHS$(=O)_2$R, -C(=O)R, -C(=O)NRR, -S$(=O)_2$OH, -S$(=O)_2$R, -OS$(=O)_2$OR, -S$(=O)_2$NR, -S(=O)R, -OP(=O)$(OR)_2$, -P(=O)$(OR)_2$, -P(=O)$(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or a 3 to 7 membered heterocyclyl ring; and

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{20} aryl, C_6-C_{20} haloaryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, C_6-C_{20} heteroaryl, or cyano, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, -NHS$(=O)_2$R, -C(=O)R, -C(=O)NRR, -S$(=O)_2$OH, -S$(=O)_2$R, -OS$(=O)_2$OR, -S$(=O)_2$NR, -S(=O)R, -OP(=O)$(OR)_2$, -P(=O)$(OR)_2$, -P(=O)$(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

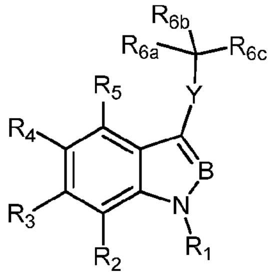
R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl which may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle; or

a pharmaceutically acceptable salt or prodrug thereof.

In another aspect, the invention provides the present invention provides a compound of formula I,



I

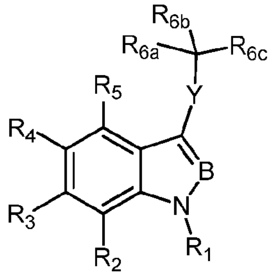
wherein

R_{6a} and R_{6b} together form 3 to 7 membered heterocycle; and

Y, B, R_1, R_2-R_5, and R_{6c} are as defined in preceding aspect;

a pharmaceutically acceptable salt or prodrug thereof.

In a fourth aspect, the invention provides the present invention provides a compound of formula I,


I

wherein

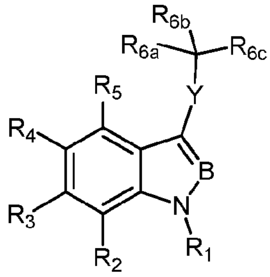
R_{6c} is cyano; and

Y, B, R_1, and R_2-R_5 are as defined in the preceding aspect; and

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or a 3 to 7 membered heterocyclyl ring

a pharmaceutically acceptable salt or prodrug thereof.

In another aspect, the present invention provides a compound of formula I,


I

wherein

Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, (C=S)NH, SCH_2, OCH_2, CH_2SO_2, OSO_2, $NHSO_2$,O(C=O), O(C=S), S(C=O), CH_2(C=O), CH_2(C=S), CH_2(C=SO_2), O(C=SO_2), NH(C=SO_2), NH(C=O), or NH(C=S);

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -Br, -F, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -

S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_2-R_5 are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, -NR$_2$, -N$^+$R$_3$, =NR, -CX$_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO$_2$, =N$_2$, -N$_3$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring; and

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{20} aryl, C_6-C_{20} haloaryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, -NR$_2$, -N$^+$R$_3$, =NR, -CX$_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO$_2$, =N$_2$, -N$_3$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl which may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, -NR$_2$, -N$^+$R$_3$, =NR, -CX$_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO$_2$, =N$_2$, -N$_3$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle; or

a pharmaceutically acceptable salt or prodrug thereof.

The following embodiments relate to any of the aspects relating to the compound of formula I above, as appropriate.

In one embodiment, R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, or C_6-C_{12} aryl, wherein each of said alkyl or aryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, or C_6-C_{12} aryl.

In one embodiment, R_{12a} and R_{12b} are each independently selected from hydrogen, methyl, ethyl, n-propyl, n-butyl, n-pentyl, or phenyl.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, $(C=O)CH_2$, $(C=S)CH_2$, $(C=SO_2)CH_2$, $(C=SO_2)O$, $(C=SO_2)NH$, (C=O)NH, or (C=S)NH, preferably Y is selected from (C=O)O, (C=S)O, SO_2CH_2, SO_2O, SO_2NH, (C=O)S, $(C=O)CH_2$, $(C=S)CH_2$, $(C=SO_2)CH_2$, $(C=SO_2)O$, $(C=SO_2)NH$, (C=O)NH, or (C=S)NH, preferably Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, (C=S)NH, CH_2(C=O), O(C=O), CH_2(C=O), or NH(C=O).

In one embodiment, Y is selected from (C=O)O, (C=O)CH_2, (C=O)NH, O(C=O), CH_2(C=O), or NH(C=O). In one embodiment, Y is selected from (C=O)O, (C=O)CH_2, (C=O)NH, O(C=O), CH_2(C=O), or NH(C=O).

In one embodiment, Y is selected from (C=O)O, (C=O)CH_2, (C=O)NH, or NH(C=O). In one embodiment, Y is selected from (C=O)O, (C=O)CH_2, or (C=O)NH. In one embodiment, Y is selected from (C=O)O or (C=O)NH. In one embodiment, Y is (C=O)NH.

In one embodiment, R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more -F,- Br, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, -$OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more -F,- Br, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, -

$S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -F, -Br, -R, =O, -OR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, $-NO_2$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, -C(=O)R, -C(=O)OR, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -F, -Br, -R, =O, -OR, $-CX_3$, -OCN, -SCN, -N=C=O, $-NO_2$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, -C(=O)R, -C(=O)OR, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_8 cyanoalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_3-C_{12} cycloalkyl, C_1-C_6

alkylene- C_6-C_{12} aryl, C_1-C_6 alkylene- C_6-C_{12} fluoroaryl, C_1-C_6 alkylene- C_3-C_{12} heterocycle, C_1-C_6 alkylene-C(=O)NRR;

wherein each of said alkyl, aryl, cycloalkyl, or heterocyclyl may be optionally substituted by one or more bromo or fluoro; and said alkyl may also be optionally substituted by one or more -CN; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl.

In one embodiment, R_1 is selected from C_1-C_6 alkyl, C_1-C_6 bromoalkyl, C_1-C_6 fluoroalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, aryl, cycloalkyl, or heterocyclyl may be optionally substituted by one or more bromo or fluoro.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl.

In one embodiment, R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, 4-cyano-1-butyl, 3,3-dimethyl-1-butyl, 1- hexyl, 1-heptyl, methylene cyclohexyl, methylene-4,4-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene-4-tetrahydropyranyl, methyleneC(O)NH(cyclohexyl), methyleneC(O)NH(t-butyl), 1-ethylene-2-(N-morpholinyl), 1-ethylene-2-(N-piperidinyl), and 1-ethylene-2-(4,4-difluoro-N-piperidinyl).

In one embodiment, R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene cyclohexyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, and methylene-4-tetrahydropyranyl.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl.

In one embodiment, R_2-R_5 are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8

alkynyl, C_1-C_8 alkoxy, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_2 is hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR; and

R_3-R_5, X, and R are as defined in the preceding embodiment.

In one embodiment, R_2 is hydrogen or halo; and

R_3-R_5, X, and R are as defined in the preceding embodiment.

In one embodiment, R_2-R_5 are each independently selected from hydrogen, SO_2, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_1-C_8 alkoxy, wherein each of said alkyl or alkoxy may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_2 is hydrogen, SO_2, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, or C_1-C_8 alkyl, wherein each of said alkyl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR; and

R_3-R_5, X, and R are as defined in the preceding embodiment.

In one embodiment, R_2 is hydrogen or halo; and

R_3-R_5, X, and R are as defined in the preceding embodiment.

In one embodiment, R_2-R_5 are each independently selected from hydrogen or halo, preferably hydrogen.

In one embodiment, R_{6a} and R_{6b} are each independently selected from C_1-C_4 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or a 3 to 7 membered heterocyclyl ring.

In one embodiment, R_{6a} and R_{6b} are each independently selected from C_1-C_4 alkyl or R_{6a} and R_{6b} together form a C_3-C_5 cycloalkyl ring, preferably methyl. In another embodiment, R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring, preferably cyclopropyl.

In one embodiment, R_{6a} and R_{6b} together form a 3 to 6 membered heterocyclyl ring.
In one embodiment, the heterocyclyl ring is a 5 or 6 membered ring.

In one embodiment, the heterocyclyl ring comprises from 3 to 6 carbon atoms, from 3 to 5 carbon atoms, or from 4 to 5 carbon atoms.

In one embodiment, the heterocyclyl ring is a 4,4-tetrahydropyranyl ring.
In one embodiment, R_{6a} and R_{6b} are each methyl or R_{6a} and R_{6b} together form a cyclopropyl or cyclopentyl ring.

In one embodiment, R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, C_6-C_{12} heteroaryl, or cyano, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{6c} is cyano.

In one embodiment, R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, or C_6-C_{12} haloaryl, wherein each of said alkyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN,

-N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, or cyano, wherein each of said alkyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, -$P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{6c} is selected from C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, C_3-C_{12} cycloalkyl, or C_3-C_{12} heterocyclyl, wherein each of said alkyl, haloalkyl, aryl, haloaryl, cycloalkyl, or heterocyclyl may be optionally substituted by one or more -X, -R, =O, -OR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, $-NO_2$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, -C(=O)R, -C(=O)OR, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{6c} is selected from C_1-C_8 alkylene heterocyclyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, or C_6-C_{12} haloaryl, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -

C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{6c} is selected from C_1-C_8 alkylene heterocyclyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, or cyano, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, -NR$_2$, -N$^+$R$_3$, =NR, -CX$_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO$_2$, =N$_2$, -N$_3$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{6c} is selected from C_1-C_8 alkylene heterocyclyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, or C_6-C_{12} haloaryl, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more halo.

In one embodiment, R_{6c} is selected from C_1-C_8 alkylene heterocyclyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, or cyano, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more halo.

In one embodiment, the C_1-C_8 alkylene heterocyclyl is C_1-C_6 alkylene heterocyclyl. In one embodiment, the C_1-C_6 alkylene heterocyclyl is methylene heterocyclyl. In one embodiment, the heterocyclyl ring is a pyrrolidinyl ring. In one embodiment, the methylene heterocyclyl is methylene pyrrolidinyl, for example methylene-N-pyrrolidinyl.

In one embodiment, the C_2-C_8 alkynyl is C_2-C_6 alkynyl. In one embodiment, the C_2-C_6 alkynyl is ethynyl.

In one embodiment, the C_6-C_{12} aryl is phenyl.

In one embodiment, the C_6-C_{12} haloaryl is halophenyl. In one embodiment, the halophenyl is chlorophenyl or fluorophenyl.

In one embodiment, R_{6c} is selected from methylene heterocyclyl, C_2-C_6 alkynyl, phenyl, halophenyl or cyano, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more halo.

In one embodiment, R_{6c} is selected from methylene pyrrolidinyl, ethynyl, phenyl, chlorophenyl, fluorophenyl, or cyano, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more halo.
In one embodiment, R_{6c} is selected from C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, C_3-C_{12} cycloalkyl, or C_3-C_{12} heterocyclyl, wherein each of said alkyl, aryl, cycloalkyl, or heterocyclyl may be optionally substituted by one or more halo.

In one embodiment, R_{6c} is selected from C_1-C_6 alkyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more halo.

In one embodiment, R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, (C=S)NH, CH_2(C=O), O(C=O), CH_2(C=O), or NH(C=O);

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, C_6-C_{12} heteroaryl, or cyano, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR,

-C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle; and

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more -F,- Br, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, Y is selected from (C=O)O, (C=O)CH_2, (C=O)NH, or NH(C=O);

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, C_6-C_{12} heteroaryl, or cyano, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle; and

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -F, -Br, -R, =O, -OR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, $-NO_2$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, -C(=O)R, -C(=O)OR, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, Y is selected from (C=O)O or (C=O)NH;

R_{6c} is selected from C_1-C_8 alkylene heterocyclyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, or cyano, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle; and

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_8 cyanoalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_6-C_{12} aryl, C_1-C_6 alkylene- C_6-C_{12} fluoroaryl, C_1-C_6 alkylene- C_3-C_{12} heterocycle, C_1-C_6 alkylene-C(=O)NRR;

wherein each of said alkyl, aryl, cycloalkyl, or heterocyclyl may be optionally substituted by one or more bromo or fluoro; and said alkyl may also be optionally substituted by one or more -CN; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_6-C_{12} aryl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo; and

R_2-R_5, R_{6a}, R_{6b}, $R_{6c,}$ R_{12a} and R_{12b} are as defined above in the second aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, $R_{6c,}$ R_{12a} and R_{12b} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are each independently selected from hydrogen or halo;

R_{6a}, R_{6b}, and $R_{6c,}$ are as defined above in the second aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, ($C=SO_2$)CH_2, ($C=SO_2$)O, ($C=SO_2$)NH, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a}, R_{6b}, and R_{6c} are as defined above in the second aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, ($C=SO_2$)CH_2, ($C=SO_2$)O, ($C=SO_2$)NH, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is as defined above in the second aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from C_1-C_6 alkyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more halo, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, heterocyclyl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from C_1-C_6 alkyl, C_6-C_{10} aryl, C_6-C_{10} haloaryl, or C_3-C_{10} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more halo, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or

a pharmaceutically acceptable salt or prodrug thereof.C_1-C_6 alkylene-

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.C_1-C_6 alkylene-

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from C_1-C_6 alkyl, C_1-C_6 bromoalkyl, C_1-C_6 fluoroalkyl, C_1-C_6 alkylene-tetrahydropyranyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is selected from CH or N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, and methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, and methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, and methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-

piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, and methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, and methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, and methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In one embodiment, Y is selected from CH_2O, SO_2O, SO_2NH, (C=O)O, (C=O)NH, or (C=S)NH;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, and methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

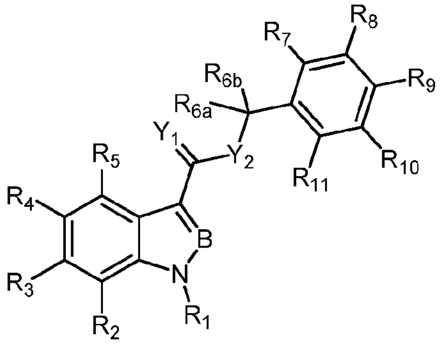
R_{6a} and R_{6b} are each independently selected from methyl; and

R_{6c} is selected from 1-pentyl, 1-hexyl, phenyl, p-fluoro-phenyl, or cyclohexyl, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y, B, R_2-R_5, R_{6a}, R_{6b}, and R_{6c} are as defined in the preceding embodiment.

In a further aspect, the present invention provides a compound of formula Ia,



Ia

wherein

Y_1 is selected from O, S, or SO_2;

Y_2 is selected from CH_2, O, or NH;

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted;

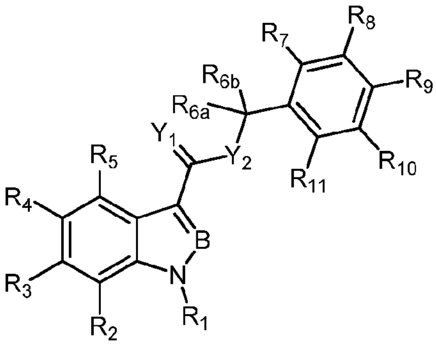
R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring; and

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted; or

a pharmaceutically acceptable salt or prodrug thereof.

In another aspect, the present invention provides a compound of formula Ia,



Ia

wherein

Y_1 is selected from O, S, or SO_2;

Y_2 is selected from CH_2, O, or NH;

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -Br, -F, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or a 3 to 7 membered heterocyclyl ring; and

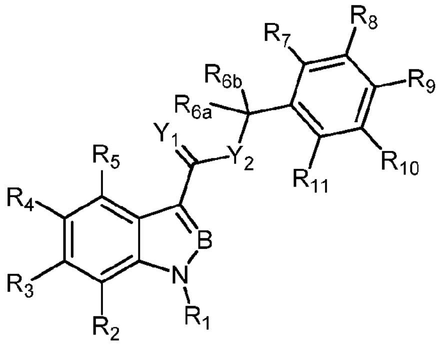
R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle; or

a pharmaceutically acceptable salt or prodrug thereof.

In another aspect, the invention provides the present invention provides a compound of formula Ia,



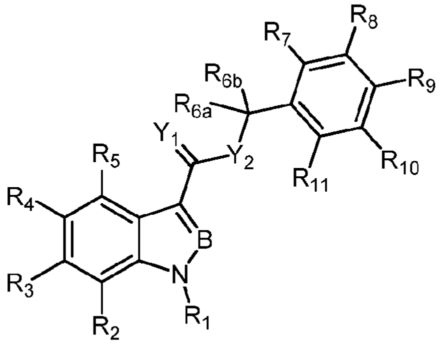
Ia

wherein

R_{6a} and R_{6b} together form 3 to 7 membered heterocycle; and

Y_1, Y_2, B, R_1, R_2-R_5 and R_7-R_{11} are as defined in the preceding aspect; a pharmaceutically acceptable salt or prodrug thereof.

In another aspect, the present invention provides a compound of formula Ia,



Ia

wherein

Y_1 is selected from O, S, or SO_2;

Y_2 is selected from CH_2, O, or NH;

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -Br, -F, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring; and

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_6-C_{20} aryl, C_3-C_{20} cycloalkyl, C_1-C_{20} heteroalkyl, C_3-C_{20} heterocyclyl, or C_6-C_{20} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more of -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle; or

a pharmaceutically acceptable salt or prodrug thereof.

The following embodiments relate to any of the aspects of the compound of formula Ia above, as appropriate.

In one embodiment, R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, or C_6-C_{12} aryl, wherein each of said alkyl or aryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$,

-S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, or C_6-C_{12} aryl.

In one embodiment, R_{12a} and R_{12b} are each independently selected from hydrogen, methyl, ethyl, n-propyl, n-butyl, n-pentyl, or phenyl.

In one embodiment, Y_1 is selected from O, S, or SO_2, preferably Y_1 is selected from O or S. In one embodiment, Y_1 is O.

In one embodiment, Y_2 is selected from CH_2, O, or NH, preferably Y_2 is selected from NH or O.

In one embodiment, Y_1 is O; and Y_2 is NH or O. In one embodiment, Y_1 is O; and Y_2 is NH.

In one embodiment, B is CH. In one embodiment, B is N.

In one embodiment, R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more -F,- Br, -R, =O, -OR, -SR, -NMeEt, -NEtEt, -N^+R_3, =NR, -CX_3, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO_2, =N_2, -N_3, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -Br, -F, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more of -Br, -F, -R, =O, -OR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, $-NO_2$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, -C(=O)R, -C(=O)OR, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_8 cyanoalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_6-C_{12} aryl, C_1-C_6 alkylene- C_6-C_{12} fluoroaryl, C_1-C_6 alkylene- C_3-C_{12} heterocycle, C_1-C_6 alkylene-C(=O)NRR;

wherein each of said alkyl, aryl, cycloalkyl, or heterocyclyl may be optionally substituted by one or more bromo or fluoro; and said alkyl may also be optionally substituted by one or more -CN; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl.

In one embodiment, R_1 is selected from C_1-C_6 alkyl, C_1-C_6 bromoalkyl, C_1-C_6 fluoroalkyl, C_6-C_{12} aryl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl.

In one embodiment, R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, 4-cyano-1-butyl, 3,3-dimethyl-1-butyl, 1- hexyl, 1-heptyl, methylene cyclohexyl, methylene-4,4-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene-4-tetrahydropyranyl, methyleneC(O)NH(cyclohexyl), methyleneC(O)NH(t-butyl), 1-ethylene-2-(N-morpholinyl), 1-ethylene-2-(N-piperidinyl), and 1-ethylene-2-(4,4-difluoro-N-piperidinyl).

In one embodiment, R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, and methylene-4-tetrahydropyranyl.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl.

In one embodiment, R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_2 is hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR; and

R_3-R_5, R_7-R_{11}, X, and R are as defined in the preceding embodiment.

In one embodiment, R_2 is hydrogen or halo; and

R_3-R_5, R_7-R_{11}, X, and R are as defined in the preceding embodiment.

In one embodiment, R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen, SO_2, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_1-C_8 alkoxy, wherein each of said alkyl or alkoxy may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

In one embodiment, R_2 is hydrogen, SO_2, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, or C_1-C_8 alkyl, wherein each of said alkyl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR; and

R_3-R_5, R_7-R_{11}, X, and R are as defined in the preceding embodiment.

In one embodiment, R_2 is hydrogen or halo; and

R_3-R_5, R_7-R_{11}, X, and R are as defined in the preceding embodiment.

In one embodiment, R_2-R_5, R_7- R_{11} are each independently selected from hydrogen or halo.

In one embodiment, R_2-R_5, R_7, R_8, R_{10}, and R_{11} are hydrogen and R_9 is halo.

In one embodiment, R_2-R_5, R_7, R_8, R_{10}, and R_{11} are hydrogen and R_9 is fluoro.

In one embodiment, R_{6a} and R_{6b} are each independently selected from C_1-C_4 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or a 3 to 7 membered heterocyclyl ring.

In one embodiment, R_{6a} and R_{6b} are each independently selected from C_1-C_4 alkyl or R_{6a} and R_{6b} together form a C_3-C_5 cycloalkyl ring.

In one embodiment, R_{6a} and R_{6b} are each methyl or R_{6a} and R_{6b} together form a cyclopropyl or cyclopentyl ring.

In one embodiment, R_{6a} and R_{6b} together form a 3 to 6 membered heterocyclyl ring.
In one embodiment, the heterocyclyl ring is a 5 or 6 membered ring.

In one embodiment, the heterocyclyl ring comprises from 3 to 6 carbon atoms, from 3 to 5 carbon atoms, or from 4 to 5 carbon atoms.

In one embodiment, the heterocyclyl ring is a 4,4-tetrahydropyranyl ring.

In one embodiment, R_{6a} and R_{6b} are each independently methyl.

In one embodiment, R_{6a} and R_{6b} together form a cyclopropyl ring.

In one embodiment, Y_1 is selected from O, S, or SO_2;

Y_2 is selected from CH_2, O, or NH; and

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more -F,- Br, -R, =O, -OR, -SR, -NMeEt, -NEtEt, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, Y_1 is O;

Y_2 is selected from NH or O; and

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -F, -Br, -R, =O, -OR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, $-NO_2$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, -C(=O)R, -C(=O)OR, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

In one embodiment, Y_1 is O;

Y_2 is selected from NH; and

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_8 cyanoalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_6-C_{12} aryl, C_1-C_6 alkylene- C_6-C_{12} fluoroaryl, C_1-C_6 alkylene- C_3-C_{12} heterocycle, C_1-C_6 alkylene-C(=O)NRR;

wherein each of said alkyl, aryl, cycloalkyl, or heterocyclyl may be optionally substituted by one or more bromo or fluoro; and said alkyl may also be optionally substituted by one or more -CN; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from CH_2, O, or NH; and

B, R_1, R_2-R_5, R_{6a}, R_{6b}, R_7-R_{11}, R_{12a} and R_{12b} are as defined above in the sixth aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O; and

B, R_1, R_2-R_5, R_{6a}, R_{6b}, R_7-R_{11}, R_{12a} and R_{12b} are as defined above in the sixth aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo; and

R_2-R_5, R_{6a}, R_{6b}, R_7-R_{11}, R_{12a} and R_{12b} are as defined above in the sixth aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, R_7-R_{11}, R_{12a} and R_{12b} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen or halo;

R_{6a}, R_{6b}, and R_7-R_{11} and R_{12a} and R_{12b} are as defined above in the sixth aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, R_7-R_{11}, R_{12a} and R_{12b} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a}, R_{6b}, and R_7-R_{11}, R_{12a} and R_{12b} are as defined above in the sixth aspect of the invention, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, R_7-R_{11}, R_{12a} and R_{12b} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, halo, C_1-C_8 alkyl, or C_1-C_8 alkoxy, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, halo, methyl, ethyl, n-propyl, methoxy, or ethoxy, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7-R_{11} are each independently selected from hydrogen, halo, methyl, ethyl, n-propyl, methoxy, or ethoxy, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7-R_{11} are each independently selected from hydrogen or halo, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, heterocyclyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_9 is halo;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_6 alkyl, C_1-C_6 bromoalkyl, C_1-C_6 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-

bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{10} aryl, or C_3-C_{10} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, heterocyclyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{12} aryl, or C_3-C_{12} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from C_1-C_6 alkyl, C_1-C_6 bromoalkyl, C_1-C_6 fluoroalkyl, C_1-C_6 alkylene-3,3-difluoro-1-cyclohexyl, C_1-C_6 alkylene-p-fluoro-phenyl, C_1-C_6 alkylene-adamantyl, C_1-C_6 alkylene-N-methyl-2-piperidinyl, C_1-C_6 alkylene-cycloheptanyl, C_1-C_6 alkylene-2-bicyclo[2.2.1]heptanyl, C_1-C_6 alkylene-tetrahydropyranyl, C_6-C_{10} aryl, or C_3-C_{10} cycloalkyl, wherein each of said alkyl, aryl, or cycloalkyl may be optionally substituted by one or more fluoro or bromo;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is C_1-C_6 alkylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is selected from CH or N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_9 is fluoro;

R_7, R_8, R_{10}, and R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-

piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl or R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-

piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} are each independently selected from methyl; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is N;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, Y_1 is selected from O or S;

Y_2 is selected from NH or O;

B is CH;

R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene cyclohexyl, or methylene-4-tetrahydropyranyl;

R_2-R_5 are hydrogen;

R_{6a} and R_{6b} together form a cyclopropyl ring; and

R_7- R_{11} are hydrogen, or

a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, R_1 is methylene-4,4-difluoro-1-cyclohexyl; and

Y_1, Y_2, B, R_2-R_5, R_{6a}, R_{6b}, and R_7-R_{11} are as defined in the preceding embodiment.

In one embodiment, the compound of the invention is SGT-23, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is SGT-24, or a pharmaceutically acceptable salt or prodrug thereof

In one embodiment, the compound of the invention is SGT-25, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is SGT-41, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is SGT-42, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is SGT-55, or a pharmaceutically acceptable salt or prodrug thereof.

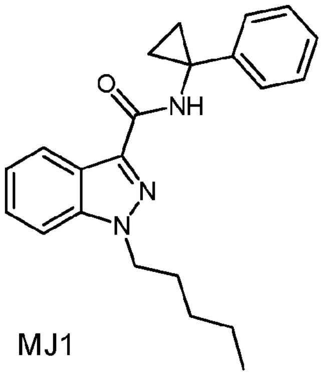
In one embodiment, the compound of the invention is SGT-56, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is SGT-60, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is SGT-65, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is SGT-67, or a pharmaceutically acceptable salt or prodrug thereof.

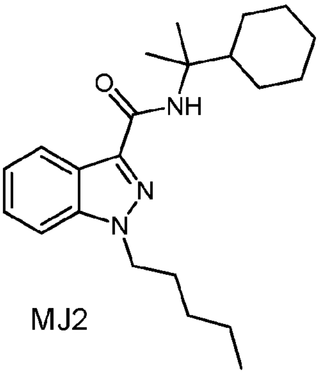
In one embodiment, the compound of the invention is



MJ1

, or a pharmaceutically acceptable salt or prodrug thereof.

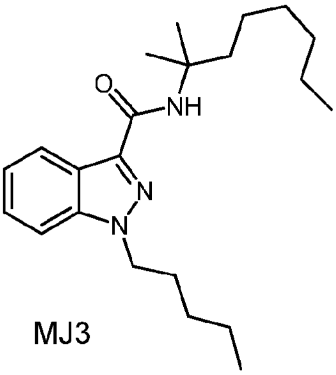
In one embodiment, the compound of the invention is



MJ2

, or a pharmaceutically acceptable salt or prodrug thereof.

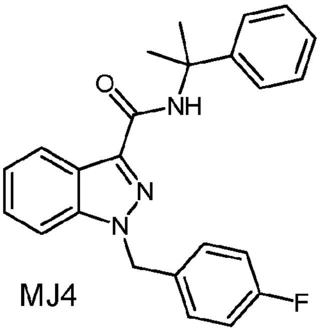
In one embodiment, the compound of the invention is



MJ3

, or a pharmaceutically acceptable salt or prodrug thereof.

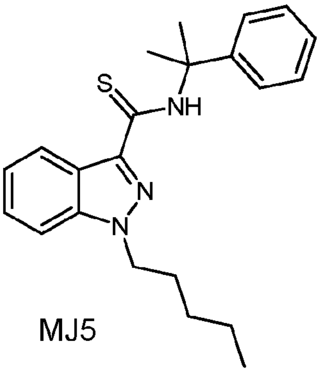
In one embodiment, the compound of the invention is



MJ4

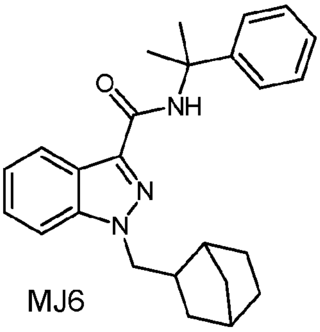
, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is


MJ5

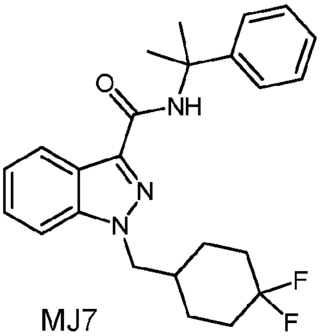
, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is


MJ6

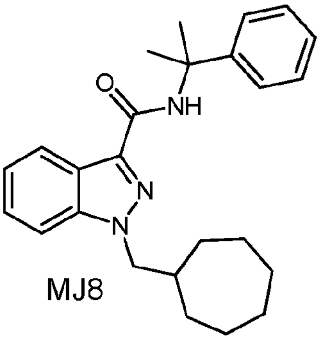
, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is


MJ7

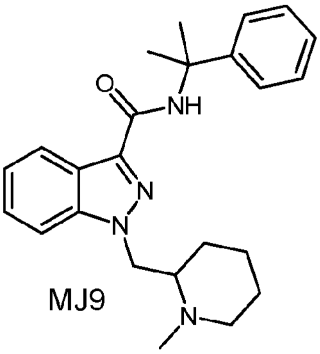
, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is


MJ8

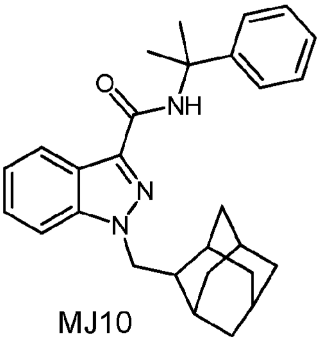
, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is


MJ9

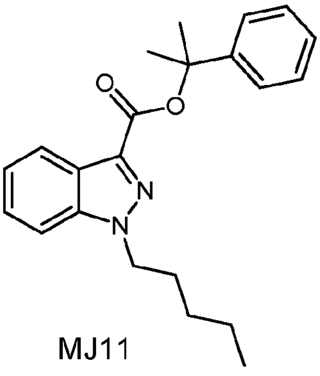
, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is


MJ10

, or a pharmaceutically acceptable salt or prodrug thereof.

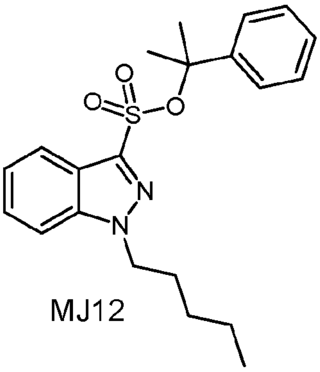
In one embodiment, the compound of the invention is



MJ11

, or a pharmaceutically acceptable salt or prodrug thereof.

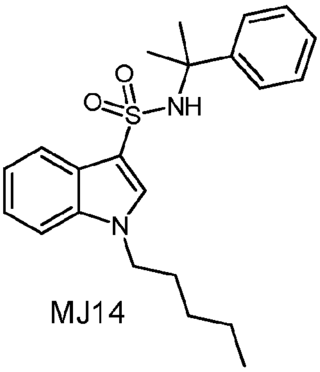
In one embodiment, the compound of the invention is



MJ12

, or a pharmaceutically acceptable salt or prodrug thereof.

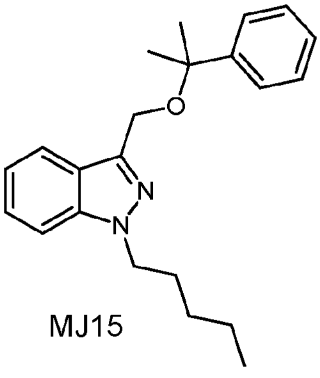
In one embodiment, the compound of the invention is



MJ14

, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is



MJ15

, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is selected from the group comprising: SGT-23, SGT-24, SGT-25, SGT-41, SGT-42, SGT-55, SGT-56, SGT-60, SGT-65, SGT-67, MJ1-MJ12, MJ14, and MJ15, or a pharmaceutically acceptable salt or prodrug thereof.

In one embodiment, the compound of the invention is selected from the compounds listed in Tables 1, 2, and 3 in the Examples, or a pharmaceutically acceptable salt or prodrug thereof. In one embodiment, the compound of the invention is selected from the compounds listed in Tables 1 and 2 in the Examples, or a pharmaceutically acceptable salt or prodrug thereof.

Asymmetric centres may exist in the compounds of the invention. The asymmetric centres may be designated by the symbols "R" or "S", depending on the configuration of substituents in three dimensional space at the chiral carbon atom. All stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and l-isomers, and mixtures thereof of the compounds are contemplated herein. Individual enantiomers of the compounds can be prepared synthetically from commercially available enantiopure starting materials or by preparing enantiomeric mixtures of the compounds and resolving the mixture into individual enantiomers. Resolution methods include conversion of the enantiomeric mixture into a mixture of diastereomers and separation of the diastereomers by, for example, recrystallisation or chromatography; direct separation of the enantiomers on chiral chromatographic columns; and any other appropriate method known in the art. Starting materials of defined stereochemistry may be commercially available or made and resolved by techniques well known in the art.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New

York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral centre(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms “racemic mixture” and “racemate” refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

The compounds of the invention may also exist as geometric isomers. All cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers, as well as the appropriate mixtures thereof of the compounds are contemplated herein.

The compounds may also exist as tautomers, for example, keto/enol; imine/enamine; amide/imino alcohol; nitroso/oxime; thioketone/enethiol; N- nitroso/hyroxyazo; and nitro/aci-nitro. All tautomeric isomers of the compounds are contemplated herein.

The compounds may also exist as isotopologues and isotopomers, wherein one or more atoms in the compounds are replaced with different isotopes. Suitable isotopes include, for example, ^{1}H, ^{2}H (D), ^{3}H (T), ^{12}C, ^{13}C, ^{14}C, ^{16}O, and ^{18}O.

The compounds may exist in solvated or unsolvated forms. If the solvent is water, the solvate may be referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, or a tri-hydrate. All solvates of the compounds are contemplated herein.

Pharmaceutically acceptable salts of the compounds of the invention are also contemplated herein. Salts of the compounds include, for example, acid addition salts, base addition salts, and quaternary salts of basic nitrogen-containing groups.

Acid addition salts can be prepared by reacting compounds, in free base form, with inorganic or organic acids. Examples of inorganic acids include, but are not limited to, hydrochloric; hydrobromic; hydroiodic; nitric; carbonic; sulfuric; and phosphoric acid. Examples of organic acids include, but are not limited to, cholic; sorbic; lauric; acetic; trifluoroacetic; formic; propionic; succinic; glycolic; gluconic; digluconic; lactic; malic; tartaric; citric; ascorbic; glucuronic; maleic; fumaric; pyruvic; aspartic; glutamic; aryl carboxylic; anthranilic acid; mesylic; stearic; salicylic; phenylacetic; mandelic; embonic (pamoic); alkylsulfonic; ethanesulfonic; arylsulfonic; benzenesulfonic; pantothenic; sulfanilic; cyclohexylaminosulfonic; β-hydroxybutyric; galactaric; galacturonic; adipic, alginic; butyric; camphoric; camphorsulfonic; cyclopentanepropionic; dodecylsulfic; glycoheptanoic; glycerophosphic; heptanoic; hexanoic; nicotinic; 2-naphthalesulfonic; oxalic; palmoic; pectinic; 3-phenylpropionic; picric; pivalic; thiocyanic; tosylic; and undecanoic acid.

Base addition salt can be prepared by reacting compounds, in free acid form, with inorganic or organic bases. Examples of base addition salts include metal salts and organic salts. Preferred metal salts include alkali metal salts, alkaline earth metal salts, and other physiologically acceptable metal salts. Preferably the metal salt comprises aluminium, calcium, lithium, magnesium, potassium, sodium, or zinc. Organic salts may be made from amines, such as trimethylamine, diethylamine, *N*,*N*'-dibenzylethylenediamine, chloroprocaine, ethanolamine, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine.

5.3 Methods of making the compounds of the invention

The abbreviations used in the general methods are defined as follows:

"LG" is an appropriate leaving group and includes halo, tosyl, triflate, mesyl, and any other highly stabilised anionic leaving group. Such leaving groups are known to those of skill in the art.

"AIBN" means azobisisobutyronitrile. "NBS" means *N*-bromo succinimide. "DCM" means dichloromethane (CH_2Cl_2). "Et" means ethyl. "EtOAc" means ethylacetate. "Me" means methyl ($-CH_3$). "MeOH" means methanol. "MeCN" means acetonitrile. "Pr" means propyl.

"i-Pr" means isopropyl (-$CH(CH_3)_2$). "i-PrOH" means isopropanol. "rt" means room temperature. "THF" means tetrahydrofuran. "TLC" means thin layer chromatography.

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups (PG) are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical PG will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PG groups do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the person skilled in the art.

Various functional groups of the compounds of the invention may be protected. For example, PGs for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical PGs in the synthetic schemes set forth herein. However, some hydroxyl and thio PGs are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl PGs and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts (John Wiley & Sons, Inc., New York, 1999, ISBN 0-471-16019-9) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages

155-184. For PGs for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other PGs for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

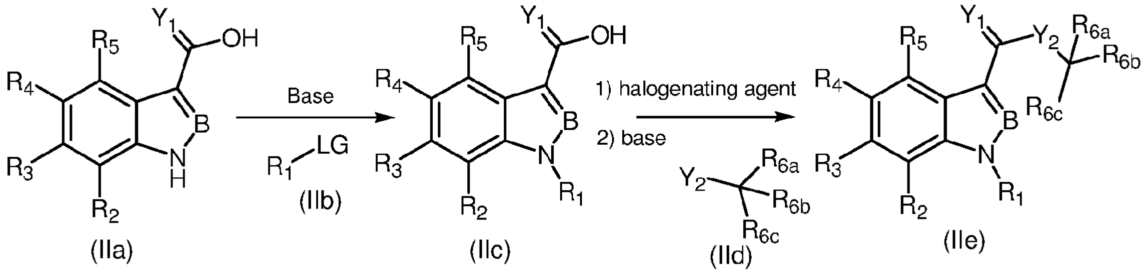
Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

The compounds of the invention may be synthesised according to the general methods described below.

General method A

Compounds of formula (IIe) can be prepared using the synthetic route detailed in Scheme 1, in which, R_1, R_2-R_5, R_{6a}-R_{6c}, Y_1, Y_2, and B are as defined for the invention and LG is an appropriate leaving group.

Scheme 1



Compounds of formula (IIa), (IIb), and (IId) can be either obtained from commercial suppliers or synthesised as needed. For example, many compounds of formula (IIb) wherein LG is halo, for example bromo, are commercially available. Alternatively, compounds of (IIb) may be prepared from their corresponding alcohols. For example, compounds of formula (IIb) wherein LG is, for example, tosyl or mesyl, may be prepared from the corresponding alcohol by reaction with p-toluene sulfonyl chloride or methane sulfonyl chloride and a base such as triethylamine in dichloromethane.

In the first step, a compound of formula (IIa) together with an appropriate base, such as sodium hydride, is stirred in an anhydrous solvent at 0°C. A solution containing compound (IIb) in an anhydrous solvent is added dropwise to the solution containing the compound of formula (IIa), and the resulting mixture is stirred at 0°C for at least 30 minutes, after which the mixture is allowed to return to room temperature and stirred for a further 30 minutes. Suitable reaction conditions would be known to one of skill in the art or could be found in *J. Med. Chem.* 1991; 34(3): 1099-1110 and *Bioorg. Med. Chem. Lett.* 1994; 4(4): 563-566.

The compound of formula (IIc) is isolated via standard work up procedures known to those of skill in the art. For example, an organic solvent and water is added to the reaction mixture containing the compound of formula (IIc). The aqueous phase is extracted with an organic solvent and the combined organic extracts washed with brine, separated, and dried over anhydrous magnesium sulfate. The combined organic extracts are then concentrated under reduced pressure and purified, as necessary, by processes known in the art, such as flash column chromatography, distillation, crystallisation, or preparative HPLC.

In the second step, a solution containing a halogenating agent, such as thionyl chloride, oxalyl chloride, or phosphorous oxychloride, in an anhydrous solvent is added dropwise to a stirred solution of compound (IIc) in the same anhydrous solvent at 0°. The resulting mixture is stirred at 0°C for at least 30 minutes, returned to room temperature, and stirred for at least 30 minutes. The mixture is then cooled to 0°C.

A solution containing compound (IId) and a base, such as triethylamine or disopropylethylamine, in the same anhydrous solvent the mixture containing the acid chloride is added dropwise to the above described mixture, and the mixture is stirred at 0° for at least thirty minutes. The mixture is then warmed to room temperature and stirred for at least 30 minutes. A saturated solution of sodium bicarbonate is then added to the reaction mixture. The compound of formula (IIe) is isolated via standard work up procedures known to those of skill in the art. For example, an organic solvent and water is added to the reaction mixture containing the compound of formula (IIc). The aqueous phase is extracted with an organic solvent and the combined organic extracts washed with brine, separated and dried over anhydrous magnesium sulfate. The combined organic extracts are then concentrated under reduced pressure and purified, as necessary, by processes known in the art, such as flash column chromatography, distillation, or preparative HPLC.

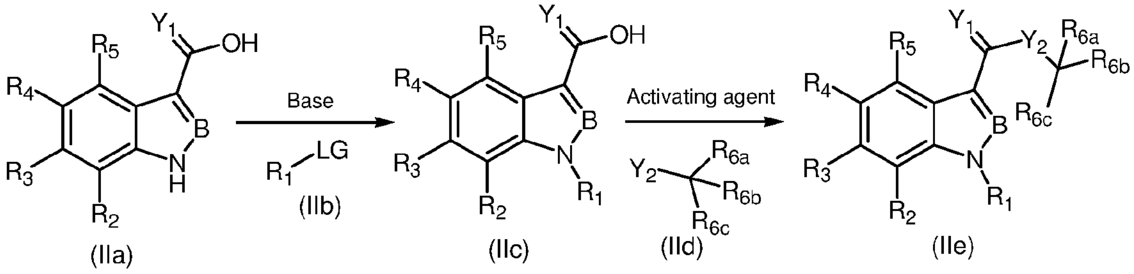
General method B

Compound of formula (IIe) can also be prepared using the synthetic route detailed in Scheme 1, in which, R_1, R_2-R_5, R_{6a}-R_{6c}, Y_1, Y_2, and B are as defined for the invention and LG is an appropriate leaving group may.

The first step of the synthesis is as described above with respect to General method A.

In the second step an activating agent, such as N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU) or N,N-dicyclohexylcarbodiimide (DCC), is added to a stirred solution of compound (IIc) and compound and in dichloromethane at 0°C. The reaction mixture is allowed to warm to room temperature and then stirred for 12 hours. In some embodiments, for example, where the activating agent is HBTU, a base such as diisopropylethylamine is added to reaction mixture following the addition of the activating agent. The order of addition of the reagents may be varied, as appropriate.

Scheme 1A

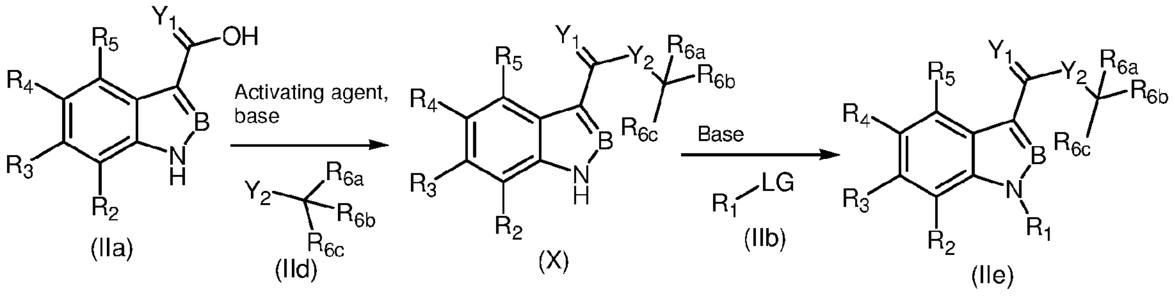


Standard work-up and, optionally, purification provide the compound of formula (IIe). For example, after stirring for 12 hours the reaction mixture is filtered through Celite, concentrated under reduced pressure , and then purified by column chromatorgraphy and then crystallisation from an appropriate solvent or mixture of solvents, for example a mixture of hexane-ethyl acetate.

General method C

Compounds of formula (IIe) can also be prepared using the synthetic route detailed in Scheme 1B, in which R_1, R_2-R_5, R_{6a}-R_{6c}, Y_1, Y_2, and B are as defined for the compounds of the invention and LG is an appropriate leaving group.

Scheme 1B



Compounds of formula (IIa), (IIb), and (IId) can either be obtained from commercial suppliers or synthesised according to standard methods known in the art as needed.

In the first step, a compound of formula (IIa) is coupled with a compound of formula (IId). The compound of formula (IIa) is treated with a suitable activating agent, for example N,N,N',N'-tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate (HBTU), in an ahydrous aprotic organic solvent, typically N,N-dimethylformamide (DMF), at ambient temperature under an atmosphere of argon. Other activating agents may be used, depending on the nature and reactivity of the compound of formula (IIb). For example, for certain compounds of formula (IIb) wherein one or more of R_2-R_5 is halo, for example fluoro, N,N-dicyclohexylcarbodiimide (DCC) may be used as the activating agent. A wide range of activating agents are known in the art for activating, for example, carboxylic acid groups for reaction with alcohols and amines.

A base, such as triethylamine or diisopropylamine, is then added dropwise at ambient temperature over suitable period of time, for example 2 hours. The period of time over which the base is added may depend on the scale of the reaction. Depending on the reactivity of the reagents, it may be desirable to cool the reaction mixture prior to and/or during addition of the base.

The reaction mixture is then stirred at ambient temperature for 15 hours before gradually heating to 120°C, for example at 25°C per hour, and then heating at 120°C for 3 hours. The progress of the reaction may be monitored by any suitable means known in the art, for example thin layer chromatography or HPLC.

Standard workup and, optionally, purification provides the compound of formula (X). For example, as described herein in the Examples, the reaction mixture is allowed to cool, the solvent removed under reduced pressure, and then saturated sodium carbonate solution added and resultant mixture cooled to below 5°C to form a precipitate. The precipitate is filtered and washed with water, triturated with saturated sodium carbonate solution, and then filtered and washed again with water. Finally, toluene is added and then evaporated to provide the compound of formula (X).

Alternative, workup and purification methods may be used as appropriate depending on the nature and reactivity of the compound of formula (X).

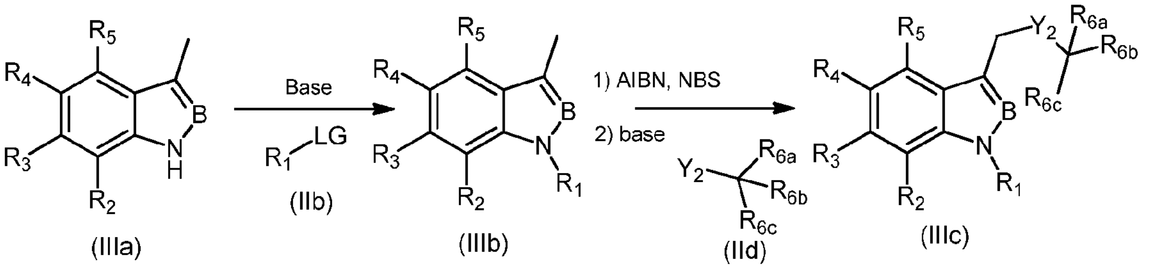
In the second step, the compound of formula (X) is coupled with a compound of formula (IIb) in the presence of a suitable base. For certain compound of formula (X), the reaction is carried out by combining the compound of formula (X) and anhydrous potassium carbonate in a suitable solvent, for example anhydrous DMF, and then adding the compound of formula (IIb) at ambient temperature. The reaction mixture is then heated at 70°C for 15 hours.

Standard workup and, optionally, purification provides the compound of formula (IIe). For example, as described herein in the Examples, the reaction mixture is allowed to cool, the solvent removed under reduced pressure, and then ethyl acetate added. The mixture is then poured onto ice and, once the ice has melted, the organic layer separated. The aqueous layer is then extracted with ethyl acetate, and the combined organic extracts washed with sodium carbonate solution, then dried over sodium sulfate and filtered. The solvent is removed, ethyl acetate added and the solution passed through silica. Fractions containing the compound of formula (IIe) are combined and the solvent removed to provide the desired compound. Other workup and purification methods may be used, as appropriate.

General method D

A compound of formula (IIIc) can be prepared using the synthetic route detailed in Scheme 2, in which, R_1, R_2-R_5, R_{6a}-R_{6c}, Y_2, and B are as defined for the invention, and LG is an appropriate leaving group.

Scheme 2



Compounds of formula (IIIa), (IIb), and (IId) can be either obtained from commercial suppliers or synthesised as needed.

A compound of formula (IIIa) together with an appropriate base, such as sodium hydride, is stirred in an anhydrous solvent at 0°C. A solution containing compound (IIb) in an anhydrous solvent is added dropwise to the solution containing the compound of formula (IIIa), and the resulting mixture is stirred at 0°C for at least 30 minutes, after which the mixture is allowed to return to room temperature and stirred for a further 30 minutes.

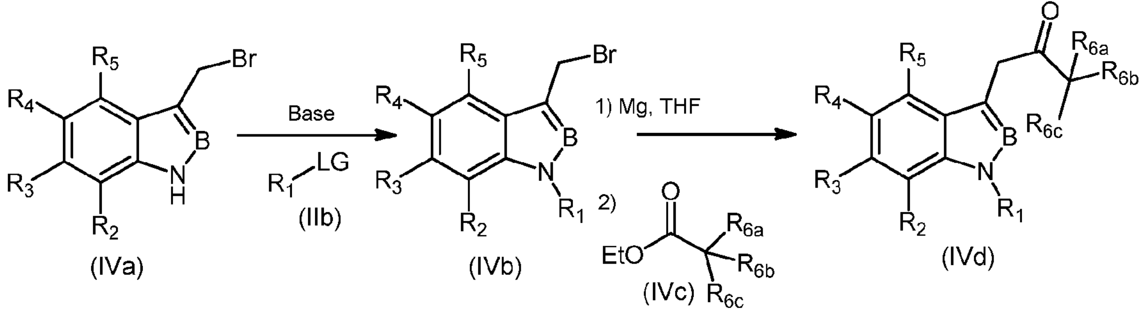
The compound of formula (IIIb) is isolated as an oil via standard work up procedures known to those of skill in the art. For example, an organic solvent and water is added to the reaction mixture containing the compound of formula (IIIb). The aqueous phase is extracted with an organic solvent and the combined organic extracts washed with brine, separated, and dried over anhydrous magnesium sulfate. The combined organic extracts are then concentrated under reduced pressure and purified, as necessary, by processes known in the art, such as flash column chromatography, distillation, or preparative HPLC.

A solution containing compound (IIIb), AIBN, and NBS in a halogenated solvent and acid is stirred at room temperature for at least five minutes, and then irradiated for at least 4 hours. Water may be added and the mixture extracted with a halogenated solvent.

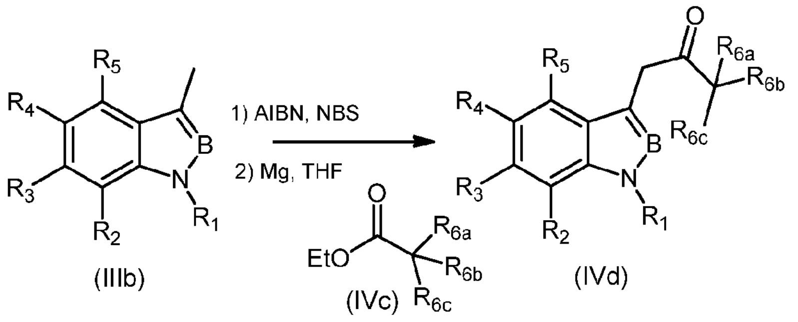
The compound of formula (IIIc) is isolated as an oil via standard work up procedures known to those of skill in the art. For example, a halogenated solvent and water is added to the reaction mixture containing the compound of formula (IIIc). The aqueous phase is extracted with a halogenated solvent and the combined organic extracts washed with brine, separated and dried over anhydrous magnesium sulfate. The combined organic extracts are then concentrated under reduced pressure and purified, as necessary, by processes known in the art, such as flash column chromatography, distillation, or preparative HPLC.

The compounds of the invention may also be synthesised according to the schemes described below using the techniques set out in general methods A and B and using reaction conditions known to those of skill in the art. In the schemes below, R_1, R_2-R_5, R_{6a}-R_{6c}, PG, and B are as defined for the invention, and LG is an appropriate leaving group.

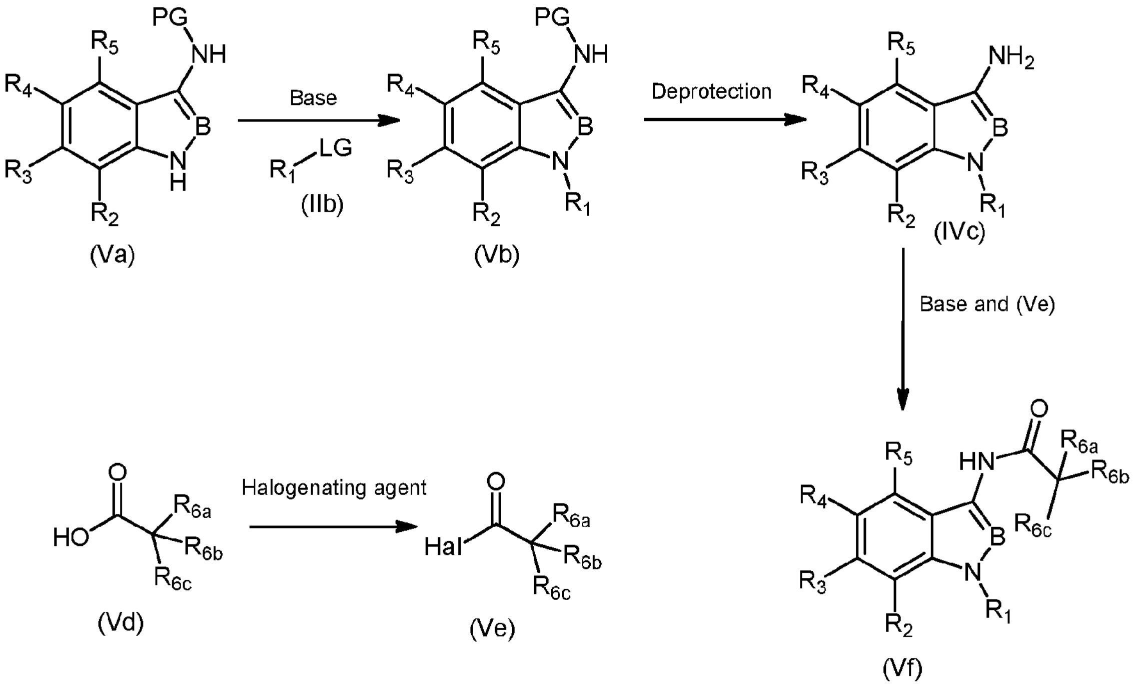
Scheme 3



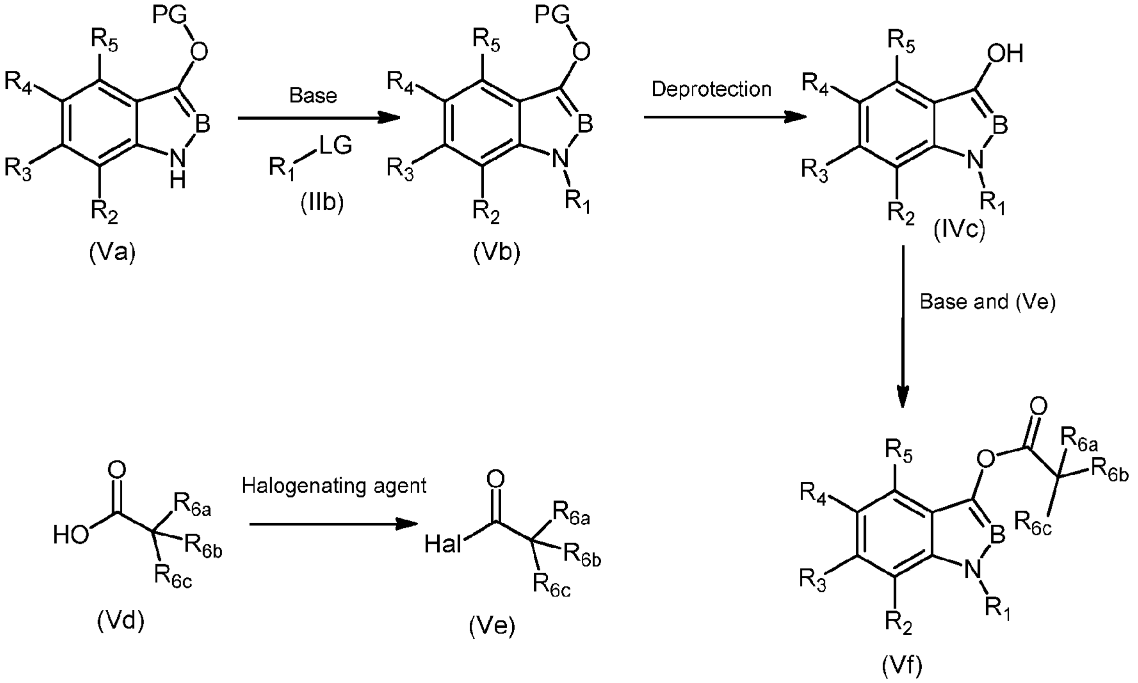
or



Scheme 4



Scheme 5



A person skilled in the art, understanding the disclosures of the general methods and specific preparation examples, would know how to modify the general methods to accommodate the different substituents that may be present on the compounds of the invention.

The embodiments of the invention described above are intended to be merely exemplary, and those skilled in the art will recognise, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific materials, compounds, and procedures. All such equivalents are considered to be within the scope of the invention as set out in the accompanying claims

5.4 Pharmaceutical compositions

The compounds of the invention can be used in a range of medicinal applications. While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical compositions. The compositions of the invention comprise one or more compounds of the present invention, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carriers must be "acceptable" in the sense of being compatible with the other ingredients of the composition and physiologically innocuous to the recipient. The carrier must also be suitable for the mode of administration of the active agent.

In one aspect, the invention relates to a pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier. Pharmaceutical compositions containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, gel, caps, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents including sweetening agents, flavouring agents, colouring agents and preserving agents, in order to provide a palatable preparation.

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain carriers, excipients, glidants, fillers, binders and the like. Aqueous compositions are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All compositions will optionally contain excipients such as those set forth in the

Handbook of Pharmaceutical Excipients (1986), herein incorporated by reference in its entirety. Carriers and excipients include methylsulfonylmethane (MSM), 2-hydroxypropyl beta-cyclodextrin, mannitol, ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the compositions ranges from about 3 to about 11, but is ordinarily about 7 to 10.

The compound of the invention may exist in a suspension. Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more colouring agents, one or more flavouring agents and one or more sweetening agents, such as sucrose or saccharin.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oil suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth herein, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavouring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such compositions may also contain a demulcent, a preservative, a flavouring or a colouring agent.

The oily phase of the emulsions may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabiliser. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabiliser(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of cream compositions.

Emulgents and emulsion stabilisers suitable for use in the composition of the invention include Tween® 20 or 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

Oral compositions

In one embodiment, the composition of the invention is an oral composition. Preferably, the composition is in the form of a pill, tablet, or dragee.

A tablet is made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient.

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable carrier, which is suitable for manufacture of tablets. These carriers may be, for example, inert diluents, such as 2-hydroxypropyl beta-cyclodextrin, methylsulfonylmethane (MSM), mannitol, calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatine or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed. In one embodiment, the composition of the invention comprises methylsulfonylmethane (MSM) as the carrier. In one embodiment, the composition of the invention comprises 2-hydroxypropyl beta-cyclodextrin as the carrier.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules (gel caps), cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

Compositions for oral use may be also presented as hard gelatine capsules (gel caps) where the active ingredient is mixed with an inert solid carrier, for example methylsulfonylmethane (MSM), 2-hydroxypropyl beta-cyclodextrin, mannitol, calcium phosphate or kaolin, or as soft gelatine capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

In one aspect, the invention provides a pharmaceutical composition for oral administration. In one embodiment, an oral pharmaceutical composition of the invention is prepared as follows: a compound of the invention is dissolved in a solvent, such as acetone or diethyl ether, and is mixed with a suitable diluent at a ratio of active ingredient:diluent of 1:99. Suitable diluents include those that are approved for use in food, dietary supplements, or tabletting, and may include 2-hydroxypropyl beta-cyclodextrin, mannitol or methylsulfonylmethane, more preferably methylsulfonylmethane. Optional carriers and/or excipients may also be added. The solvent may then be removed.

The resulting powder may be then divided up into capsules or pressed into tablets.

Inhalable compositions

The compounds are of the invention are also absorbed when administered by inhalation. In one embodiment, the composition of the invention is a nasal, e-liquid, or vaporiser composition. Compositions suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 μm (including particle sizes in a range between 0.1 and 500 μm in increments such as 0.5 μm, 1 μm, 30 μm, 35 μm, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable compositions include aqueous or oily solutions of the active ingredient. Compositions suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other suitable therapeutic agents.

In one aspect, the invention provides an inhalable composition comprising a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. In one embodiment, an inhalable composition of the invention is prepared as follows: a compound of the invention is dissolved in a solution of water and propylene glycol, and optionally a surfactant, a fungicide, and/or a bacteriostatic agent. Preferably, the ratio of propylene glycol:water may be in the range of 0.5:10 to 3:10, preferably 1.5:10. Preferably, the ratio of surfactant:water may be in the range of 0.001:10 to 0.5:10, preferably 0.05:10. Preferably, the surfactant, if present, may be Tween 20.

A compound of the invention is dissolved initially in propylene glycol with stirring. Optionally, a surfactant, a fungicide, and/or a bacteriostatic agent is then added followed by water. Preferably, the mixture is heated with stirring to ensure the compound of the invention dissolves into solution. After cooling, the mixture is administered nasally.

An e-cigarette is an electronic inhaler that vaporises a liquid solution (e-liquid) into an aerosol mist, simulating the act of tobacco smoking.

In one aspect, the invention provides an e-liquid comprising a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. In one embodiment, the e-liquid is a mixture of propylene glycol and glycerine, preferably vegetable glycerine. In one embodiment, the e-liquid has a preferred ratio of propylene glycol:glycerine may be from 1:1 to 4:1, more preferably 3:2. In one embodiment, the e-liquid further comprises a flavour enhancer, such as Tasty Puff or similar.

In one embodiment, the e-liquid optionally includes a surfactant to enhance solubility. The surfactant may be present at a concentration of between 0.01% and 5% by weight, more preferably 0.5% by weight. The surfactant may be chosen from the group consisting of Triton X- 100, Tween 20 and Tween 60, more preferably Tween 20.

In one embodiment, an e-liquid of the invention may be prepared as follows: the compound of the invention is dissolved in propylene glycol, which may be at room temperature or heated. Preferably, the propylene glycol is heated to 60-90 °C, preferably 80 ° C, with stirring until the compound of the invention is in solution.

Vegetable glycerine, and optionally a surfactant, is added with stirring, and the mixture is allowed to slowly return to room temperature. The mixture may be filtered.

A smoking composition is intended to be smoked in a cigarette or pipe.

In one aspect, the invention provides a smoking composition comprising a compound of the invention, or a pharmaceutically acceptable salt or prodrug thereof, and a pharmaceutically acceptable carrier. In one embodiment, a smoking composition of the invention is prepared as follows: the compound of the invention is dissolved in acetone and then mixed with a base herb in a large mixing machine.

The base herb is selected from damiana, marshmallow, mugwort, passionflower, lion's tail, blue lotus, calea zacatechichi and salvia divinorum, more preferably damiana. Optionally, food colours are added to the acetone solution to colour the final product.

The mixture is mixed for approximately 30-60 minutes, preferably approximately 40 minutes to ensure even distribution of the compound of the invention through the base herb.

The wet mixture is dried to remove the acetone. The dry mixture is then ready for packing and use.

Optionally, the dry mixture is sprayed with flavouring agents, which are dissolved in a propylene glycol and/or ethanol base. Preferably, the mixture is mixed in a mixing machine after being sprayed with a flavouring agent, and then dried for approximately 30 minutes before packing and use.

A preferred blend contains 500g of the compound of the invention and 1kg of powdered food colour (e.g. Brilliant Blue) dissolved in 6 litres of acetone sprayed onto 25kg of damiana. The mixture is then dried over a 12 hour period before being sprayed with 2.5 litres of "Tasty Puff" flavour liquid.

The blend may be smoked or used in a vaporiser.

Topical compositions

The compounds of the invention may be administered topically, for example in a cream. In one embodiment, the composition of the invention is a topical composition. Preferably, the composition is in the form of an ointment, cream, eye drop, or paste.

The choice of suitable oils or fats for a topical composition is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as

Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical compositions may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogues.

Compositions suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such compositions in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

For administration to the eye or other external tissues e.g., mouth and skin, the compositions are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavoured basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatine and glycerine, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier. In one embodiment, the composition of the invention is an oral topical composition, preferably the composition is in the form of a lozenge.

Injectable compositions

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilised powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

In one embodiment, the composition of the invention is an injectable composition.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the composition isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

Other compositions of the invention

Compositions for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray compositions containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Controlled release compositions of the invention

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provides compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

In one embodiment, the composition of the invention is a time-release composition.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release composition intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per millilitre (ml) of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Unit dosage forms of the compositions of the invention

The pharmaceutical compositions of the invention include those suitable for the foregoing administration routes. The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.), herein incorporated by reference in its entirety. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

The compositions are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage compositions are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients provided by the present invention the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example those suitable for oral administration may include flavouring agents.

Dosages of the compound of the invention

The effective dose of an active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical composition, and will be determined by the clinician using conventional dose escalation studies. The effective dose can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about 0.01 to about 5 mg/kg body weight per day. More typically, from about 0.05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 0.01 mg to 1000 mg, or between 0.05 mg and 500 mg, and may take the form of single or multiple doses.

In one embodiment, the composition of the invention is in a dosage form which contains at least 0.001 mg of the compound of the invention, preferably 0.005, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 150, 160, 170, 180, 190, 200, 250, 300, 350, 400, 450, or 500 mg of the compound of the invention.

In one embodiment, the composition of the invention is in a dosage form which contains 0.001-500 mg of the compound of the invention, preferably 0.005-500, 0.01-500, 0.05-500, 0.1-500, 0.2-500, 0.3-500, 0.4-500, 0.5-500, 0.6-500, 0.7-500, 0.8-500, 0.9-500, 1-500, 2-500, 3-500, 4-500, 5-500, 6-500, 7-500, 8-500, 9-500, 10-500, 15-500, 20-500, 25-500, 30-500, 35-500, 40-500, 45-500, 50-500, 60-500, 75-500, 80-500, 85-500, 90-500, 95-500, 100-500, 110-500, 120-500, 130-500, 140-500, 150-500, 150-500, 160-500, 170-500, 180-500, 190-500, 200-500, 250-500, 300-500, 350-500, 400-500, or 450-500 mg of the compound of the invention.

In one embodiment, the dosage form is in an inhalable, topical, oral, smokable, or injectable dosage form.

In one embodiment, the composition of the invention is an e-liquid which contains at least 0.1 mg/ml of the compound of the invention, preferably 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 150, 160, 170, 180, 190, or 200 mg/ml of the compound of the invention.

In one embodiment, the composition of the invention is an e-liquid which contains 0.1-200 mg/ml of the compound of the invention, preferably 0.5-200, 1-200, 2-200, 3-200, 4-200, 5-200, 6-200, 7-200, 8-200, 9-200, 10-200, 15-200, 20-200, 25-200, 30-200, 35-200, 40-200, 45-200, 50-200, 60-200, 75-200, 80-200, 85-200, 90-200, 95-200, 100-200, 110-200, 120-200, 130-200, 140-200, 150-200, 150-200, 160-200, 170-200, 180-200, or 190-200 mg/ml of the compound of the invention.

In one embodiment, the composition of the invention is a smoking composition which contains at least 0.1 mg/g of the compound of the invention, preferably 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 150, 160, 170, 180, 190, or 200 mg/g of the compound of the invention.

In one embodiment, the composition of the invention is smoking composition which contains 0.1-200 mg/g of the compound of the invention, preferably 0.5-200, 1-200, 2-200, 3-200, 4-200, 5-200, 6-200, 7-200, 8-200, 9-200, 10-200, 15-200, 20-200, 25-200, 30-200, 35-200, 40-200, 45-200, 50-200, 60-200, 75-200, 80-200, 85-200, 90-200, 95-200, 100-200, 110-200, 120-200, 130-200, 140-200, 150-200, 150-200, 160-200, 170-200, 180-200, or 190-200 mg/g of the compound of the invention.

In one embodiment, the composition of the invention is an inhalable composition which contains at least 1 mg/ml of the compound of the invention, preferably 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 60, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 150, 160, 170, 180, 190, or 200 mg/g of the compound of the invention.

In one embodiment, the composition of the invention is an inhalable composition which contains 0.1-200 mg/ml of the compound of the invention, preferably 0.5-200, 1-200, 2-200, 3-200, 4-200, 5-200, 6-200, 7-200, 8-200, 9-200, 10-200, 15-200, 20-200, 25-200, 30-200, 35-200, 40-200, 45-200, 50-200, 60-200, 75-200, 80-200, 85-200, 90-200, 95-200, 100-200, 110-200, 120-200, 130-200, 140-200, 150-200, 150-200, 160-200, 170-200, 180-200, or 190-200 mg/ml of the compound of the invention.

5.5 Uses of the compounds of the invention

The compounds of the invention bind to CB_1 and/or CB_2 receptors. Compounds that bind to these receptors are known to have gastrointestinal, cardiovascular, and/or central nervous system activity.

In one embodiment, the compound of the invention is a CB_1 and/or CB_2 receptor agonist.

In one embodiment, the EC50 of the compound of the invention in a CB_1 and/or CB_2 receptor affinity assay is less than about 1000 μM, 500 μM, 250 μM, 100 μM, 50 μM, 25 μM, 10 μM, 5 μM, 3 μM, 1 μM, 750 nM, 500 nM, 400 nM, 300 nM, 200 nM, 100 nM, 90 nM, 80 nM, 70 nM, 60 nM, 50 nM, 40 nM, 20 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.9 nM, 0.8 nM, 0.7 nM, 0.6 nM, 0.5 nM, 0.4 nM, 0.3 nM, 0.2 nM, 0.1 nM, 0.05 nM, 0.01 nM, 0.001 nM, or 0.0001 nM, and useful ranges may be selected between any of these values.

In one embodiment, the EC50 is from about 0.0001 nM to about 1000 μM, from about 0.0001 nM to about 100 μM, from about 0.0001 to about 10 μM, from about 0.001 nM to about 500 μM, from about 0.001 nM to about 100 μM, from about 0.001 nM to about 50 μM, from about 0.001 nM to about 10 μM, from about 0.001 nM to about 5 μM, from about 0.01 nM to about 500 μM, from about 0.01 nM to about 100 μM, from about 0.01 nM to about 50 μM, from about 0.01 nM to about 10 μM, from about 0.01 nM to about 5 μM, from about 0.05 nM to about 500 μM, from about 0.05 nM to about 100 μM, from about 0.05 nM to about 50 μM, from about 0.05 nM to about 10 μM, or from about 0.05 nM to about 5 μM.

In one embodiment, the CB_1 and/or CB_2 receptor affinity assay measures the effect of the compound on cAMP modulation using the HTRF detection method. In one embodiment, the CB_1 and/or CB_2 receptor affinity assay is substantially as described herein in the Examples.

The inventors have advantageously found that certain compounds of formula (I) exhibit selective affinity for CB_1 and/or CB_2.

In one embodiment, the compound of the invention is a selective CB_1 and/or CB_2 receptor agonist.

In one embodiment, the compound of the invention is selective for CB_1 and/or CB_2 over at least one G-protein coupled receptor or ligand-gated ion channel selected from the group consisting of adenosine A1, adenosine A2A, adenosine A3, adrenergic α1, adrenergic α2, adrenergic β1, adrenergic β2, angiotensin AT1, central benzodiazepine BZD, bradykinin B2, cholecystokinin CCK1, dopamine D1, dopamine D2S, endothelin ETA, GABA (non-selective), galanin GAL2, chemokine CXCR2, chemokine CCR1, histamine H1, histamine H2, melatonin MT1, muscarininc M1, muscarininc M2, muscarininc M3, tachykinin NK2, tachykinin NK3, neuropeptide Y1, neuropeptide Y2, neurotensin NTS1, opioid μ, opioid δ, opioid κ, opioid NOP, prostaglandin EP4, serotonin 5-HT1A, serotonin HT1B, serotonin HT2A, serotonin HT2B, serotonin HT3, serotonin HT5A, serotonin HT6, serotonin HT7, somatostatin SST, vasoactive intestinal polypeptide VPAC1, vasopressin V1A, Ca2+ channel L, KV channel, SKCa channel, Na+ channel (site 2), Cl- channel (GABA-gated), noradrenaline transporter, dopamine transporter, and serotonin transporter.

In one embodiment, the compounds are selective for CB_1 and/or CB_2 over all of the aforementioned G-protein coupled receptors and ligand-gated ion channels.

In one embodiment, the compounds is at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 100, 125, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, 1000, 1250, 1500, 1750, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 6000, 7000, 8000, 9000, or 10000 times more selective for CB_1 and/or CB_2 than for the G-protein coupled receptor or ligand-gated ion channel.

Selectivity may be measured by any suitable method known in the art, for example by comparing the Ki or EC50 of the compound for CB_1 and/or CB_2 with the Ki or EC50 of the compound for the G-protein coupled receptor or ligand-gated ion channel.

In one embodiment, the compound has an inhibition of control specific binding of less than about 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1% and/or a control specific binding of at least 40, 50, 60, 70, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% for at least one G-protein coupled receptor or ligand-gated ion channel selected from the group consisting of adenosine A1, adenosine A2A, adenosine A3, adrenergic α1, adrenergic α2, adrenergic β1, adrenergic β2, angiotensin AT1, central benzodiazepine BZD, bradykinin B2, cholecystokinin CCK1, dopamine D1, dopamine D2S, endothelin ETA, GABA (non-selective), galanin GAL2, chemokine CXCR2, chemokine CCR1, histamine H1, histamine H2, melatonin MT1, muscarininc M1, muscarininc M2, muscarininc M3, tachykinin NK2, tachykinin NK3, neuropeptide Y1, neuropeptide Y2, neurotensin NTS1, opioid μ, opioid δ, opioid κ, opioid NOP, prostaglandin EP4, serotonin 5-HT1A, serotonin HT1B, serotonin HT2A, serotonin HT2B, serotonin HT3, serotonin HT5A, serotonin HT6, serotonin HT7, somatostatin SST, vasoactive intestinal polypeptide VPAC1, vasopressin V1A, Ca2+ channel L, KV channel, SKCa channel, Na+ channel (site 2), Cl- channel (GABA-gated), noradrenaline transporter, dopamine transporter, and serotonin transporter.

In one embodiment, the compound has an inhibition of control specific binding of less than about 65, 60, 55, 50, 45, 40, 35, 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1% and/or a control specific binding of at least 40, 50, 60, 70, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% for all of the aforementioned G-protein coupled receptors and ligand-gated ion channels.

In one embodiment, the inhibition of control specific binding and/or control specific binding is measured using a reference radioligand for each G-protein coupled receptor and ligand-gated ion channel.

In one embodiment, the reference radioligand is as defined in Table 6 below.
In one aspect, the invention relates to a use of a compound of the invention in the manufacture of a medicament for treating pain in a subject.

In another aspect, the invention related to use of a compound of the invention in the manufacture for treating nausea and/or emesis in a subject.

In another aspect, the invention relates to a use of a compound of the invention in the manufacture of a medicament for stimulating appetite in a subject.

In another aspect, the invention relates to a use of a compound of the invention in the manufacture of a medicament for inducing a euphoric effect in a subject.

In another aspect, the invention relates to a use of a compound of the invention in the manufacture of a medicament for relaxing a subject in a subject.

In another aspect, the invention relates to a use of a compound of the invention in the manufacture of a medicament for inducing a positive mood change in a subject.

In another aspect, the invention relates to a method of treating pain in a subject, the method comprising administering a therapeutically effective amount of a compound of the invention to the subject.

In another aspect, the invention relates to a method for treating nausea and/or emesis in a subject, the method comprising administering a therapeutically effective amount of a compound of the invention to the subject.

In another aspect, the invention relates to a method for stimulating appetite in a subject, the method comprising administering a therapeutically effective amount of a compound of the invention to the subject.

In another aspect, the invention relates to a method of inducing a euphoric effect in a subject, the method comprising administering a therapeutically effective amount of a compound of the invention to the subject.

In another aspect, the invention relates to a method of relaxing a subject, the method comprising administering a therapeutically effective amount of a compound of the invention to the subject.

In another aspect, the invention relates to method of inducing a positive mood change in a subject, the method comprising administering a therapeutically effective amount of a compound of the invention to the subject.

In another aspect, the invention relates to a compound of the invention for use in treating pain in a subject.

In another aspect, the invention relates to a compound of the invention for use in treating nausea and/or emesis in a subject.

In another aspect, the invention relates to a compound of the invention for use in stimulating appetite in a subject.

In another aspect, the invention relates to a compound of the invention for use in inducing a euphoric effect in a subject.

In another aspect, the invention relates to a compound of the invention for use in relaxing a subject.

In another aspect, the invention relates to a compound of the invention for use in inducing a positive mood change in a subject.

In the above aspects:

In one embodiment, the nausea and/or emesis is caused by injury, pain, cancer, AIDS, tuberculosis, glaucoma, menstruation, hepatitis, chemotherapy, radiotherapy, or headaches (such as muscle tension headaches, eyes strain headaches, migraines, or cluster headaches).

In one embodiment, the appetite is stimulated to treat loss of appetite caused by wasting. Preferably, the wasting is caused by cystic fibrosis, anorexia, old age, cancer, AIDS, tuberculosis, chronic diarrhoea, or cachexia, preferably cancer cachexia.

In one embodiment, the pain is selected from nociceptive pain, neuropathic pain, or psychogenic pain. In one embodiment, the nociceptive pain is caused by: inflammation, joint pain (such as arthritis, osteoarthritis, rheumatoid arthritis, or repetitive strain injury), headaches (such as muscle tension headaches, eyes strain headaches, migraines, or cluster headaches), back pain (such as back pain caused by slipped or bulging discs, spinal stenosis, compression fractures (such as those associated with osteoporosis), soft tissue damage, traumatic fractures, or structural deformities (such as scoliosis, kephosis, or lordosis)), fibromyalgia, surgery, or trauma. In one embodiment, the neuropathic pain is caused by: multiple sclerosis, phantom limb pain, peripheral (diabetic) neuropathy, post-mastectomy pain, sciatica, spinal cord injury (such as bulging or slipped discs or trauma), carpel tunnel syndrome, cancer, radiotherapy, chemotherapy, radiation injury, surgery, or HIV- associated peripheral neuropathy. In one embodiment, the psychogenic pain is caused by: headache, muscle pain, back pain, or stomach pain. In one embodiment, the pain is atypical or neuropathic pain. In one embodiment, the pain is phantom limb pain.

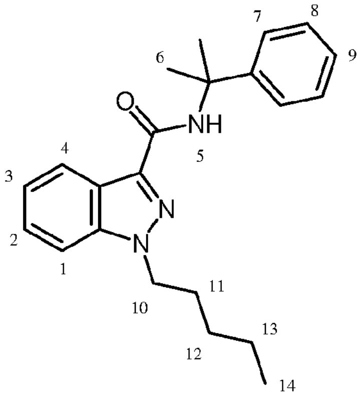
One or more compounds of the invention (herein also referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with, for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Although the present invention is broadly as defined above, those persons skilled in the art will appreciate that the invention is not limited thereto and that the invention also includes embodiments of which the following description gives examples.

6. EXAMPLES

6.1 Compounds of the invention

SGT-24

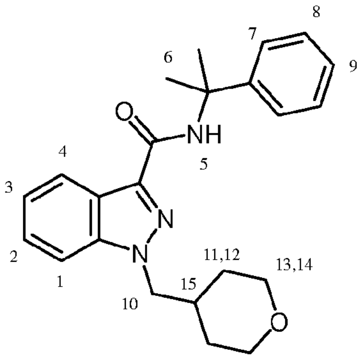


SGT-24 was synthesised according to Scheme 1 (as shown above).

1-Pentyl-1H-indazole-3-carboxylic acid (IIc) was prepared by reaction of commercially available indazole-3-carboxylic acid (IIa) with 1-bromopentane (IIb) in the presence of sodium hydride in dimethylformamide. Reaction conditions were as set out in *J. Med. Chem.* 1991; 34(3): 1099-1110 and *Bioorg. Med. Chem. Lett.* 1994; 4(4): 563-566.

Oxalyl dichloride (5.74 g, 45.2 mmol) was slowly added to a stirred solution of 1-pentyl-1H-indazole-3-carboxylic acid (10.0 g, 43.0 mmol) in dichloromethane (100 mL) at 0°C in an ice-bath. The reaction was stirred for 30 minutes. Triethylamine (9.0 mL, 64.58 mmol) was then added, followed by 2-phenylpropan-2-amine (5.82g, 43.0 mmol). The reaction was stirred for 1 hour and monitored by TLC. The reaction was diluted with water and separated into phases. The organic layer was washed with water (2x100 mL), brine (2x100 mL), dried ($MgSO_4$), and concentrated. The resulting oil was purified by flash column chromatography using petroleum ether:ethyl acetate 60:1 as eluent. 11.7 g (78%) of SGT-24 was obtained as a light yellow oil in a 78% yield. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.01 (1H, d, H1), 7.97 (1H, s, H5), 7.74 (1H, d, H4), 7.43 (1H, ddd, H2), 7.38 (1H, dd, H3), 7.19 (2H, m, H7), 4.48 (2H, t, H8), 1.90 (2H, m, H11), 1.74 (6H, m, H6), 1.25 (6H, m, H12, H10, H13), and 0.84 (3H, t, H14). MS (ESI+) m/z 350 (MH+).

SGT-42



SGT-42 was synthesised according to Scheme 1B (as shown above).

N-(1-Methyl-1-phenylethyl)-1*H*-indazole-3-carboxamide

1*H*-Indazole-3-carboxylic acid (100 g, 0.617 mol, 1.0 molar eq.) in anhydrous *N*,*N*-dimethylformamide (DMF)(10 volumes, 1 L) was mixed with cumylamine (89 mL, 1.0 molar eq.) and HBTU (281 g, 1.2 molar eq.) at room temperature under argon. To this mixture was added *N*,*N*-diisopropylethylamine (215 mL, 2.0 molar eq.) drop wise over a period of at least 2 hours. The reaction mixture was then stirred for at least 15 hours at ambient temperature under an argon blanket. The reaction mixture was the gradually heated in increments of 25°C per hour up to an internal temperature of 120°C. Once the reaction mixture reached 120°C, it was continuously heated at an internal temperature of 120°C for at least 3 hours. The reaction mixture was rotary evaporated to remove the DMF that a bath temperature of 80°C under reduced pressure. The crude product was placed in an ice bath and mixed with saturated sodium carbonate solution (10 volumes, 1 L). The resultant mixture was continuously stirred and the ice bath until the internal temperature dropped below 5°C. A beige coloured precipitate formed that was filtered and washed with cold purified water (10 x 2.5 volumes, 10 x 250 mL). The wet filter cake was then triturated in saturated sodium carbonate solution (5 volumes, 500 mL) for at least one hour at room temperature. The suspension was then filtered and rinsed with purified water (5 x 1 volume, 5 x 100 mL). The resultant product was dried under air vacuum, and then co-evaporated with toluene four times prior to final drying on a rotary evaporator with a bath temperature of 60°C to constant weight.

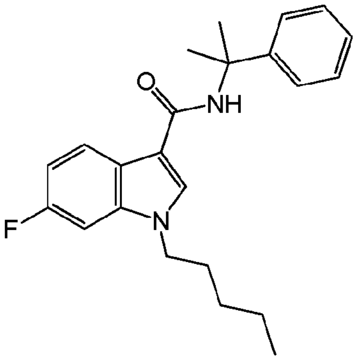
N-(1-Methyl-1-phenylethyl)-1-[(tetrahydro-2*H*-pyran-4-yl)methyl]-1*H*-indazole-3-carboxamide (SGT-42)

The quantity of reagents and materials used in the following procedure were based on the quantity of *N*-(1-Methyl-1-phenylethyl)-1*H*-indazole-3-carboxamide obtained in the preceding step, as indicated.

A solution of *N*-(1-methyl-1-phenylethyl)-1*H*-indazole-3-carboxamide (1.0 molar eq.) in anhydrous DMF (5 volumes) was mixed with anhydrous potassium carbonate (5.84 molar eq.). (Tetrahydro-2*H*-pyran-4-yl) methyl 4-methylbenzenesulfonate (1 molar eq.) was added portion wise over a period of 5 minutes at ambient temperature to the reaction mixture. The resulting reaction mixture was heated to 70°C for at least 15 hours using an oil bath. The reaction mixture was evaporated at a 40°C bath temperature under reduced pressure to remove the DMF. The evaporated residue was mixed with ethyl acetate (5 volumes) and then poured into ice (5 weight equivalents). The mixture was stirred until the ice melted. The bilayer was separated and the aqueous layer extracted with ethyl acetate (4 x 3 volumes). The combined extracts were washed with 50% saturated sodium carbonate solution (4 x 1 volume), then dried over sodium sulfate and filtered. The filtrate was evaporated at a 40° bath temperature and co-evaporated with ethyl acetate (3 x 2.5 volumes). The resultant residue was redissolved and hot ethyl acetate (4 volumes) and filtered through 60 angstrom silica (2.5 volumes) topped with a layer of anhydrous sodium sulphate. The filter bed was washed with hot ethyl acetate (2 volumes per fraction) until all of the product was released. Product containing fractions were evaporated with a bath temperature of 40°C. The crude product was triturated with methyl tert-butyl ether (MTBE)(2 volumes) at room temperature of the 2 hours, and then in an ice bath for one hour. The suspension was filtered, then rinsed with cold MTBE (4 x 1 volume). The resulting white solid was then dried under vacuum to constant weight. mp 112.7 ± 0.5 . IR ν_{max}/cm^{-1} 3328, 1664 (amide). ^1H NMR (400 MHz, DMSO-d6) δ 8.03 (1H, d, H1), 7.97 (1H, s, H5), 7.82 (1H, d, H4), 7.41-7.44 (3H, m, H2, H3), 7.33 (2H, dt, H8), 7.20 (2H, dd, H7), 4.41 (2H, d, H10), 3.84 (2H, d, H13), 3.25 (2H, m, H14), 2.23 (1H, m, H15), 1.74 (6H , s, H6), and 1.39 (4H, m, H11, H12). MS (ESI+) m/z 378 (MH+). Anal. Calcd for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7.21; N, 11.13. Found: C, 73.44; H, 7.22; N, 11.23.

^1H and ^{13}C NMR scans for SGT-42 are provided in Figures 1 and 2, respectivley.

SGT 174



SGT 174 was synthesized according to Scheme 1A (as shown above) by the following general procedure.

Alkylation of an indole-3-carboxylic acid or indazole-3-carboxylic acid (IIa)

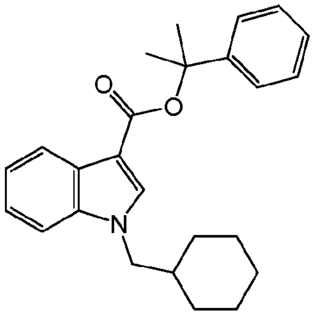
An indole-3-carboxylic acid or indazole-3-carboxylic acid (IIa)(0.1 mol) was dissolved in DMF (100 ml), and treated with NaH (0.2 mol) at 0°C. R^1Br (IIb)(0.15 mol) was added in one portion and the mixture stirred at 0°C for 1 hour. Ice water was added, and the mixture extracted with CH_2Cl_2 (3x100 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. Crystallisation from EtOAc/Hexane gave the desired 1-alkyl-indole-3-carboxylic acid or 1-alkyl-indazole-3-carboxylic (IIc) as solid.

Formation of amide (IIe)

The 1-alkyl-indole-3-carboxylic acid or 1-alkyl-indazole-3-carboxylic (IIc)(1.0 mmol) and amine (IId)(1.0 mmol) were dissolved in CH_2Cl_2 (5 ml). The mixture was cooled with ice-water. DCC (1.0 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and then stirred over night. The reaction mixture was then filtered through celite and the filtrate concentrated under vacuum. The resultant residue was purified by column chromatography. Crystallization from EtOAc/Hexane gave pure (IIe).

^1H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.90 (m, 1H), 7.41-7.27 (m, 6H), 7.15 (m, 1H), 4.51 (m, 2H), 1.82 (s, 6H), 1.74 (m, 2H), 1.31-1.29 (m, 4H), 0.90 (m, 3H).

SGT-211



SGT 211 was synthesized according to Scheme 1A (as shown above) by the following general procedure.

Alkylation of an indole-3-carboxylic acid or indazole-3-carboxylic acid (IIa) to provide the desired 1-alkyl-indole-3-carboxylic acid or 1-alkyl-indazole-3-carboxylic (IIc) was carried out according to the general procedure described above for SGT 174.

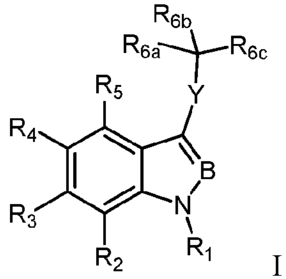
Formation of ester (IIe)

The 1-alkyl-indole-3-carboxylic acid or 1-alkyl-indazole-3-carboxylic (IIc)(1.0 mmol) and alcohol (IId)(1.0 mmol) were dissolved in acetonitrile (5 ml). The mixture was cooled with ice-water. DCC (1.0 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and then stirred over night. The reaction mixture was then filtered through celite and the filtrate concentrated under vacuum. The resultant residue was purified by column chromatography. Crystallization from EtOAc/Hexane gave pure (IIe).

^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 4.36 (m, 1H), 4.15 (m, 2H), 1.82 (s, 6H), 1.45-1.27 (m, 11H).

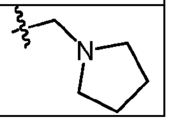
Compounds of formula I of the invention as shown in Table 1 and compounds of formula Ia were synthesised in an analogous fashion according to the general methods described herein. The aforementioned preparative procedures are representative of the procedures used.

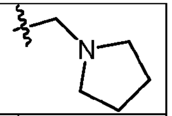
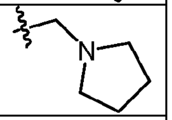
Compounds of formula I of the invention as shown in Table 3 may be synthesised in a similar manner.

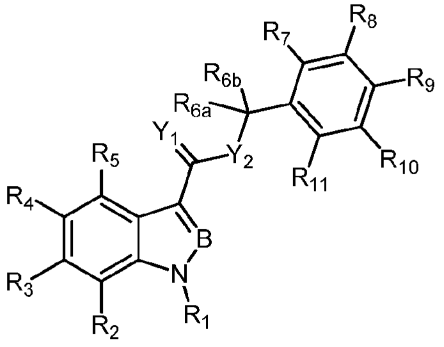


I

Table 1.

Compound	Y	B	R_1	R_2	R_3	R_4	R_5	R_{6a}	R_{6b}	R_{6c}
SGT-227	CONH	CH	1-pentyl	H	H	H	H	Me	Me	ethynyl
SGT-228	CONH	CH	5-fluoro-1-pentyl	H	H	H	H	Me	Me	ethynyl
SGT-229	CONH	CH	methylene cyclohexyl	H	H	H	H	Me	Me	ethynyl
SGT-230	CONH	CH	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	ethynyl
SGT-231	CONH	N	1-pentyl	H	H	H	H	Me	Me	ethynyl
SGT-232	CONH	N	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	ethynyl
SGT-238	CONH	CH	1-pentyl	H	H	H	H	Me	Me	cyano
SGT-241	CONH	N	1-pentyl	H	H	H	H	Me	Me	cyano
SGT-244	CONH	CH	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	cyano
SGT-239	CONH	CH	1-pentyl	H	H	H	H	Me	Me	

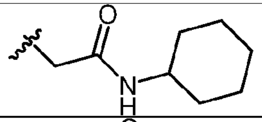
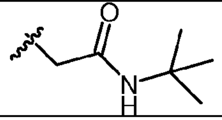
SGT-242	CONH	N	1-pentyl	H	H	H	H	Me	Me	
SGT-245	CONH	CH	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	
SGT-250	NHCO	CH	1-pentyl	H	H	H	H	Me	Me	phenyl

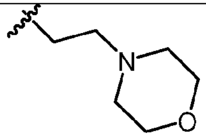


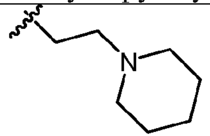
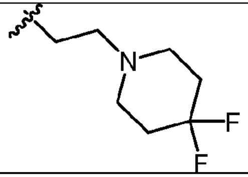
Ia

Table 2.

Compound	Y1	Y2	B	R1	R2	R3	R4	R5	R6a	R6b	R7	R8	R9	R10	R11
SGT-23	O	NH	N	1-butyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-24	O	NH	N	1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-25	O	NH	N	5-fluoro-1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-41	O	NH	N	methylene cyclohexyl	H	H	H	H	Me	Me	H	H	H	H	H

SGT-42	O	NH	N	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-55	O	NH	CH	1-butyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-56	O	NH	CH	1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-60	O	NH	N	1-pentyl	H	H	H	H	Me	Me	H	H	F	H	H
SGT-64	O	NH	CH	5-fluoro-1-pentyl	H	H	H	H	Me	Me	H	H	F	H	H
SGT-65	O	NH	N	5-fluoro-1-pentyl	H	H	H	H	Me	Me	H	H	F	H	H
SGT-67	O	NH	CH	5-fluoro-1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-78	O	NH	N	4-cyano-1-butyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-113	O	NH	N		H	H	H	H	Me	Me	H	H	H	H	H
SGT-114	O	NH	N		H	H	H	H	Me	Me	H	H	H	H	H
SGT-148	O	NH	N	3,3-dimethylbutyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-153	O	NH	CH	1-pentyl	H	H	H	H	Me	Me	H	H	Cl	H	H
SGT-154	O	NH	CH	5-fluoro-1-pentyl	H	H	H	H	Me	Me	H	H	Cl	H	H
SGT-155	O	NH	CH	methylene cyclohexyl	H	H	H	H	Me	Me	H	H	Cl	H	H
SGT-156	O	NH	CH	methylene cyclohexyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-157	O	NH	N	1-pentyl	H	H	H	H	Me	Me	H	H	Cl	H	H
SGT-158	O	NH	N	5-fluoro-1-pentyl	H	H	H	H	Me	Me	H	H	Cl	H	H

SGT-159	O	NH	N	methylene cyclohexyl	H	H	H	H	Me	Me	H	H	Cl	H	H
SGT-161	O	NH	CH	1-pentyl	H	H	H	H	cyclopropyl		H	H	H	H	H
SGT-162	O	NH	N	5-fluoro-1-pentyl	H	H	H	H	cyclopropyl		H	H	H	H	H
SGT-163	O	NH	N	methylene cyclohexyl	H	H	H	H	cyclopropyl		H	H	H	H	H
SGT-164	O	NH	CH	1-pentyl	H	H	F	H	Me	Me	H	H	H	H	H
SGT-172	O	NH	CH	1-pentyl	H	H	F	H	Me	Me	H	H	Cl	H	H
SGT-173	O	NH	CH	1-pentyl	H	H	F	H	cyclopropyl		H	H	H	H	H
SGT-174	O	NH	CH	1-pentyl	H	F	H	H	Me	Me	H	H	H	H	H
SGT-182	O	NH	CH	1-pentyl	H	F	H	H	Me	Me	H	H	Cl	H	H
SGT-183	O	NH	CH	1-pentyl	H	F	H	H	cyclopropyl		H	H	H	H	H
SGT-184	O	NH	N		H	H	H	H	Me	Me	H	H	H	H	H
SGT-185	O	NH	N	1-propyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-186	O	NH	N	1-hexyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-187	O	NH	N	1-heptyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-188	O	NH	CH	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-205	O	NH	CH	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	H	H	Cl	H	H
SGT-206	O	NH	N	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	H	H	Cl	H	H

SGT-207	O	NH	CH	methylene-4-tetrahydropyranyl	H	H	H	H	cyclopropyl		H	H	H	H	H
SGT-208	O	NH	N	methylene-4-tetrahydropyranyl	H	H	H	H	cyclopropyl		H	H	H	H	H
SGT-209	O	O	CH	1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-210	O	O	CH	5-fluoro-1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-211	O	O	CH	methylene cyclohexyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-212	O	O	CH	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-214	O	O	N	5-fluoro-1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-215	O	O	N	methylene cyclohexyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-216	O	O	N	methylene-4-tetrahydropyranyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-234	O	NH	N		H	H	H	H	Me	Me	H	H	H	H	H
SGT-235	O	NH	N		H	H	H	H	Me	Me	H	H	H	H	H
SGT-236	O	CH_2	CH	1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H
SGT-240	O	NH	CH	1-pentyl	H	H	H	H	4,4-tetrahydropyranyl		H	H	H	H	H
SGT-243	O	NH	N	1-pentyl	H	H	H	H	4,4-tetrahydropyranyl		H	H	H	H	H
SGT-246	O	NH	CH	methylene-4-	H	H	H	H	4,4-		H	H	H	H	H

				tetrahydropyranyl					tetrahydropyranyl						
SGT-247	O	NH	CH	1-pentyl	H	H	H	H	cyclopentyl		H	H	H	H	H
SGT-248	O	NH	N	1-pentyl	H	H	H	H	cyclopentyl		H	H	H	H	H
SGT-249	O	NH	CH	methylene-4-tetrahydropyranyl	H	H	H	H	cyclopentyl		H	H	H	H	H
MJ1 (SGT-160)	O	NH	N	1-pentyl	H	H	H	H	cyclopropyl		H	H	H	H	H
MJ4 (SGT-149)	O	NH	N	methylene-p-fluorophenyl	H	H	H	H	Me	Me	H	H	H	H	H
MJ6 (SGT-152)	O	NH	N	methylene-2-bicyclo[2.2.1]heptanyl	H	H	H	H	Me	Me	H	H	H	H	H
MJ9 (SGT-150)	O	NH	N	methylene-N-methyl-2-piperidinyl	H	H	H	H	Me	Me	H	H	H	H	H
MJ11 (SGT-213)	O	O	N	1-pentyl	H	H	H	H	Me	Me	H	H	H	H	H

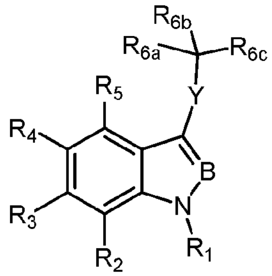


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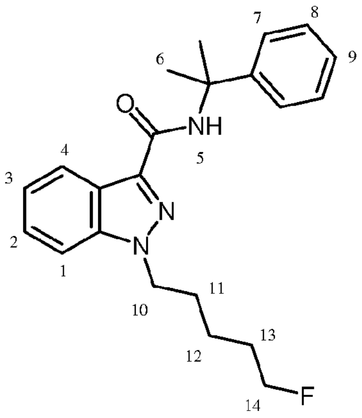
Table 3.

Compound	Y	B	R_1	R_2	R_3	R_4	R_5	R_{6a}	R_{6b}	R_{6c}
MJ2	CONH	N	1-pentyl	H	H	H	H	Me	Me	cyclohexyl
MJ3	CONH	N	1-pentyl	H	H	H	H	Me	Me	1-hexyl
MJ5	CSNH	CH	1-pentyl	H	H	H	H	Me	Me	phenyl
MJ7	CONH	N	methylene-4,4-difluoro-1-cyclohexyl	H	H	H	H	Me	Me	phenyl
MJ8	CONH	N	methylene-cycloheptanyl	H	H	H	H	Me	Me	phenyl
MJ10	CONH	N	methylene-adamantyl	H	H	H	H	Me	Me	phenyl
MJ12	SO_2O	N	1-pentyl	H	H	H	H	Me	Me	phenyl
MJ14	SO_2O	CH	1-pentyl	H	H	H	H	Me	Me	phenyl
MJ15	CH_2O	N	1-pentyl	H	H	H	H	Me	Me	phenyl

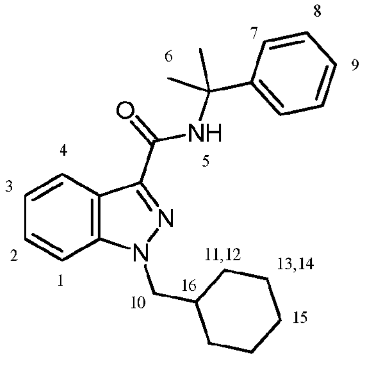
Characterisation data

^{1}H NMR for selected compounds of the invention is as shown below. MS data is also provided for selected compounds.



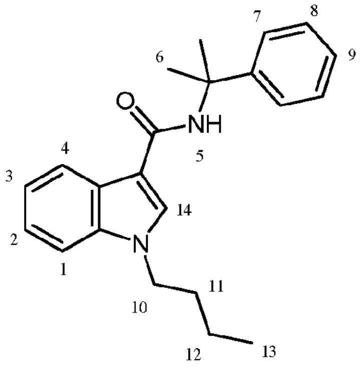
SGT-25

^{1}H NMR (400 MHz, DMSO-d6) δ 8.07 (1H, d, H1), 7.99 (1H, s, H5), 7.92 (1H, d, H4),7.72 (3H, s, H2), 7.40 (2H,s, H3), 7.38 (2H, dt, H), 4.46 (1H, m, H10), 4.31 (2H, s, H14), 2.00-1.39 (12H, m, H10, H11, H12, H13)



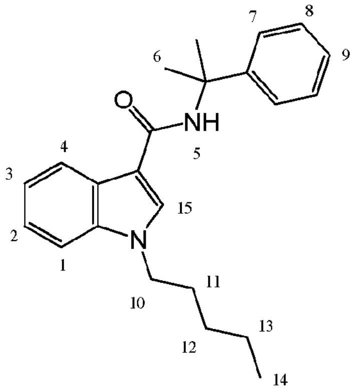
SGT-41

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (1H, d, H1), 7.45 (2H, d, H5), 7.41-7.35 (5H, m, H2, H3, H4), 7.22 (2H, m, H7), 4.28 (2H, d, H11), 1.80 (6H, s, H6), and 1.75-0.75 (12H, m, H11, H12, H13, H14, H15, H16). MS m/z 376 (MH+).



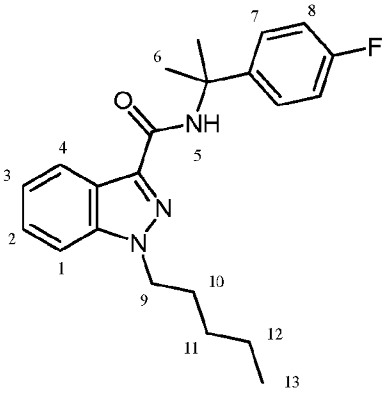
SGT-55

^{1}H NMR (400 MHz, DMSO-d6) δ 8.07 (1H, s, H14), 7.97 (1H, d, H1), 7.52 (1H, s, H5), 7.41 (1H, d, H2), 7.38 (2H,s, H3), 7.24 (2H, dt, H8), 7.12 (2H, dd, H7), 7.06 (1H, t, H9), 4.18 (2H, t, H10), 1.77 (2H, m, H11), 1.65 (6H, s, H6), 1.28 (2H, m, H12), and 0.89 (H3, t, H13). MS (ESI+) m/z 335 (MH+).



SGT-56

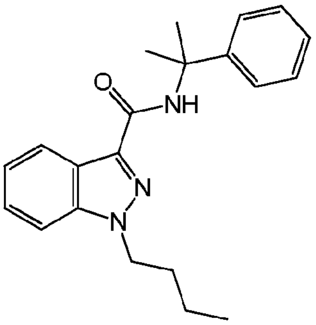
^{1}H NMR (400 MHz, DMSO-d6) δ 8.22 (1H, s, H15), 7.99 (1H, d, H4), 7.52 (1H, s, H5), 7.49 (1H, d, H1), 7.38 (1H, d, H3), 7.34 (2H, t, H2), 7.12 (2H, dd, H7), 7.06 (1H, t, H9), 4.17 (2H, t, H10), 1.77 (2H, m, H11), 1.65 (6H, s, H6), 1.31 (4H, m, H12, H13), and 0.90 (H3, t, H14).



SGT-60

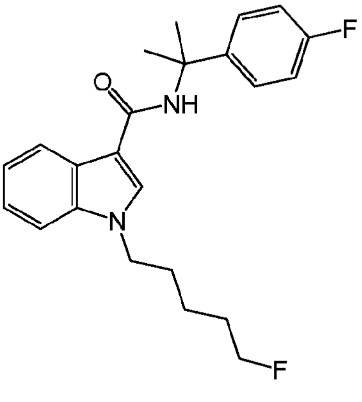
^{1}H NMR (400 MHz, DMSO-d6) δ 8.07 (1H, d, H1), 7.98 (1H, s, H1), 7.52 (1H, d, H5), 7.41 (1H, d, H4), 7.38 (1H,s, H3), 7.42 (2H, dt, H2), 7.20 (1H, dd, H7), 4.48 (2H, t, H9), 1.85 (2H, q, H11), 1.70 (6H, s, H6), 1.30-1.23 (4H, m, H12), and 0.84 (H3, t, H13).

SGT-23



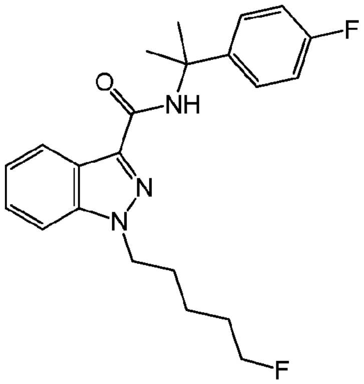
^{1}H NMR (400 MHz, DMSO-d6) δ 8.01 (dd, *J*=6.0, 1.2Hz, 1H), 7.96 (s, 1H), 7.73 (dd, *J*=6.0, 1.2Hz, 1H), 7.44 (m, 1H), 7.39 (m, 1H), 7.18 (m, 2H), 4.47 (m, 2H), 1.90 (m, 2H), 1.74 (s, 6H), 1.25 (m, 4H), 0.84 (t, 3H)

SGT-64



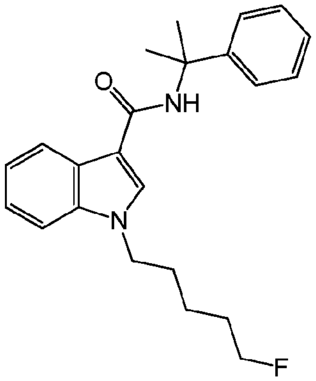
^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (m, 1H), 7.68 (s, 1H), 7.45 (m, 1H), 7.27 (m, 1H), 7.38 (m, 1H), 7.42 (m, 2H), 7.20 (m, 2H), 4,50 (m, 1H), 4.36 (m, 1H), 4.12 (m, 2H), 1.90 (m, 2H), 1.82 (s, 6H), 1.70 (m, 2H), 1.45 (m, 2H).

SGT-65



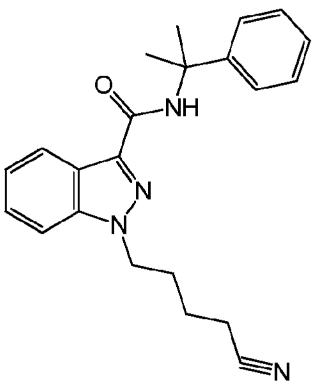
^{1}H NMR (400 MHz, DMSO-d6) δ 8.17 (dd, *J*=6.0, 1.2Hz, 1H), 7.98 (s, 1H), 7.52 (m, 1H), 7.41 (m, 1H), 7.38 (m, 1H), 7.42 (m, 2H), 7.20 (m, 1H), 4,50 (m, 1H), 4.40 (m, 3H), 1.85 (m, 2H), 1.70 (s, 6H), 1.70-1.50 (m, 4H).

SGT-67



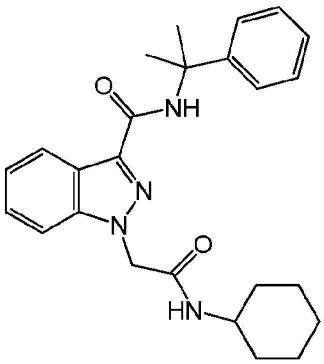
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 4.47 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 4.36 (m, 1H), 4.15 (m, 2H), 1.90 (m, 2H), 1.82 (s, 6H), 1.70 (m, 2H), 1.45 (m, 2H).

SGT-78



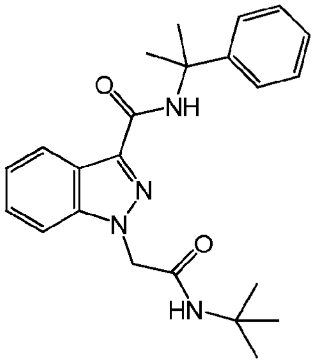
^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (m, 1H), 8.03 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4,50 (m, 2H), 1.87 (m, 2H), 1.74 (m, 2H), 1.66 (m, 2H), 1.70 (s, 6H).

SGT-113



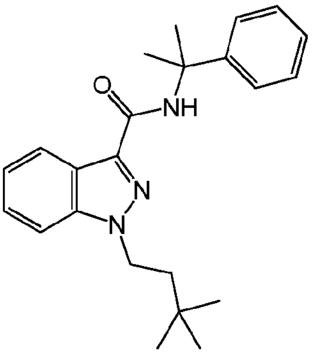
^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (m, 1H), 8.02 (s, 2H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.71 (m, 2H), 3.54 (m, 1H), 1.82 (s, 6H), 1.69-1.11 (m, 10H).

SGT-114



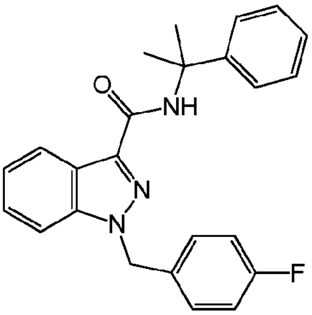
^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (m, 1H), 8.02 (s, 2H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 5.60 (m, 2H), 1.82 (s, 6H), 1.69 (s, 9H).

SGT-148



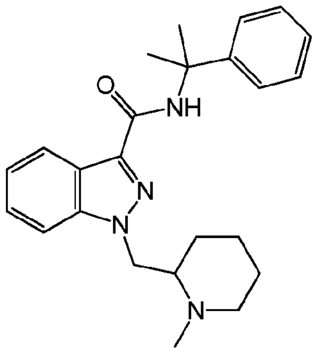
^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (m, 1H), 8.02 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.51 (m, 2H), 1.82 (s, 6H), 1.69 (m, 2H), 0.94 (s, 9H).

SGT-149



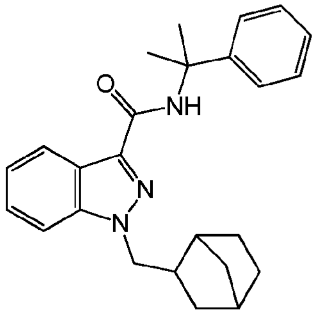
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 8.02 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.21 (m, 2H), 7.20 (m, 1H), 7.12 (m, 2H), 5.51 (m, 2H), 1.82 (s, 6H).

SGT-150



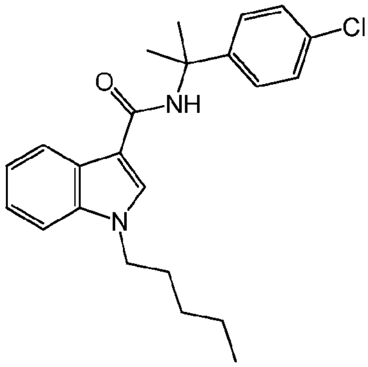
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 8.02 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.51 (m, 2H), 2.51 (m, 2H), 2.26 (s, 3H), 2.22 (m, 1H), 1.82 (s, 6H), 1.69-1.47 (m, 6H).

SGT-152



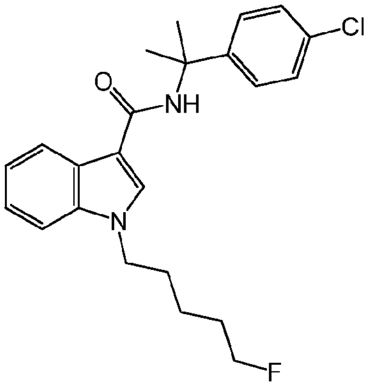
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 8.03 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.50 (m, 2H), 2.13 (m, 1H), 1.88 (m, 1H), 1.82 (s, 6H), 1.58-1.40 (m, 9H).

SGT-153



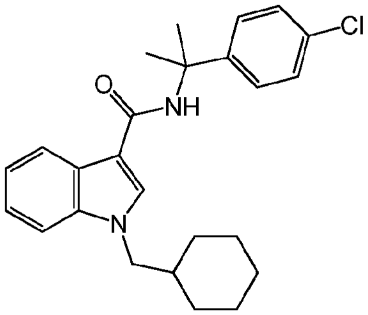
^{1}H NMR (400 MHz, DMSO-d6) δ 7.88 (m, 1H), 7.69 (s, 1H), 7.41 (m, 3H), 7.29 (m, 4H), 6.26 (s, 1H), 4.11 (m, 2H), 1.90 (m, 2H), 1.82 (s, 6H), 1.32 (m, 4H), 0.88 (m, 3H).

SGT-154



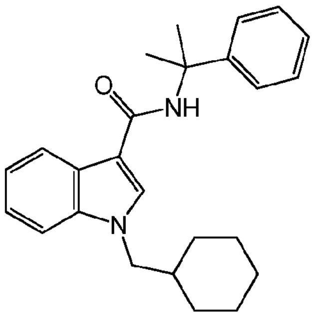
^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (m, 1H), 7.68 (s, 1H), 7.42 (m, 3H), 7.29 (m, 4H), 6.26 (s, 1H), 4,49 (m, 1H), 4.35 (m, 1H), 4.13 (m, 2H), 1.90 (m, 2H), 1.82 (s, 6H), 1.70 (m, 2H), 1.45 (m, 2H).

SGT-155



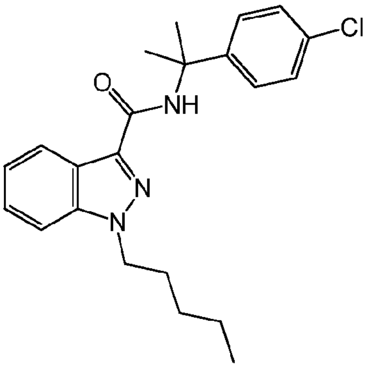
^{1}H NMR (400 MHz, DMSO-d6) δ 7.89 (m, 1H), 7.65 (s, 1H), 7.42 (m, 3H), 7.29 (m, 4H), 6.25 (s, 1H), 3.95 (m, 2H), 1.82 (s, 6H), 1.80 (m, 1H), 1.70-1.50 (m, 5H), 1.15 (m, 3H), 1.00 (m, 2H).

SGT-156



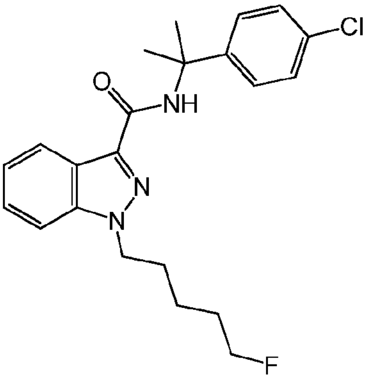
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 4.47 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 3.95 (m, 2H), 1.82 (s, 6H), 1.80 (m, 1H), 1.70-1.50 (m, 5H), 1.15 (m, 3H), 1.00 (m, 2H).

<u>SGT-157</u>



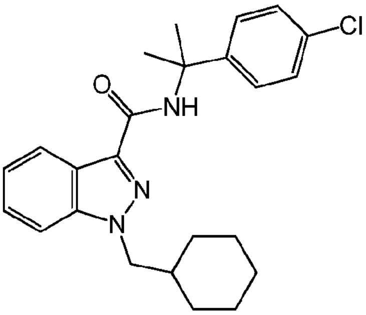
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 7.45-7.35 (m, 5H), 7.30-7.18 (m, 3H), 4.38 (m, 2H), 1.95 (m, 2H), 1.83 (s, 6H), 1.35 (m, 5H).

<u>SGT-158</u>



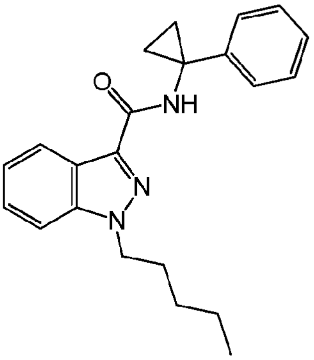
^{1}H NMR (400 MHz, DMSO-d6) δ 8.30 (m, 1H), 7.45-7.35 (m, 5H), 7.30-7.18 (m, 3H), 4.50 (m, 1H), 4.39 (m, 3H), 2.00 (m, 2H), 1.83 (s, 6H), 1.75 (m, 2H), 1.50 (m, 2H).

<u>SGT-159</u>



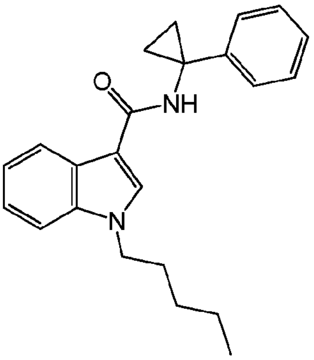
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 7.45-7.35 (m, 5H), 7.30-7.18 (m, 3H), 4.20 (m, 2H), 2.03 (m, 1H), 1.83 (s, 6H), 1.75-1.50 (m, 5H), 1.25-1.00 (m, 5H).

SGT-160



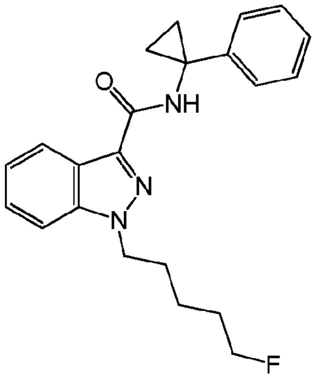
^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (m, 1H), 8.04 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.51 (m, 2H), 1.74 (m, 2H), 1.31-1.29 (m, 4H), 0.90 (m, 3H), 0.85 (m, 2H), 0.60 (m, 2H).

SGT-161



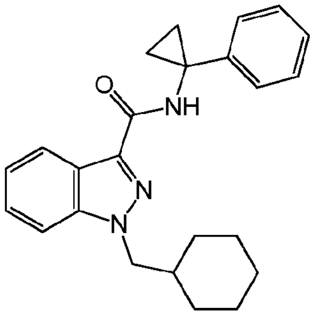
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 6.25 (s, 1H), 4.51 (m, 2H), 1.74 (m, 2H), 1.31-1.29 (m, 4H), 0.90 (m, 3H), 0.85 (m, 2H), 0.60 (m, 2H).

SGT-162



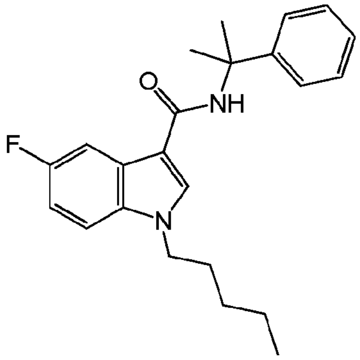
^{1}H NMR (400 MHz, DMSO-d6) δ 8.33 (m, 1H), 8.00 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4,48 (m, 1H), 4.36 (m, 1H), 4.15 (m, 2H), 1.75 (m, 2H), 1.50 (m, 2H), 1.29 (m, 2H), 0.85 (m, 2H), 0.60 (m, 2H).

SGT-163



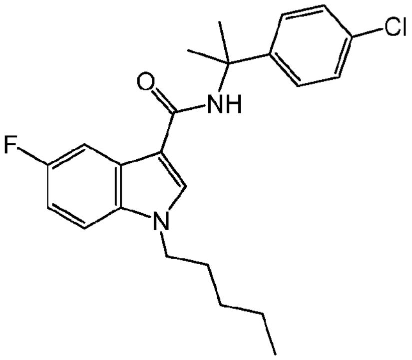
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 8.04 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.51 (m, 2H), 1.45-1.27 (m, 11H), 0.85 (m, 2H), 0.60 (m, 2H).

SGT-164



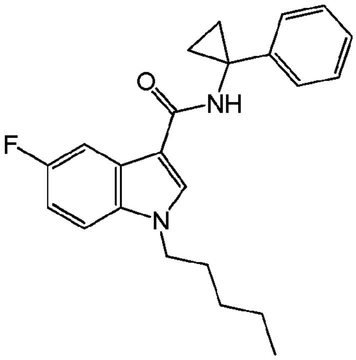
^{1}H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 8.01 (s, 1H), 7.84 (m, 1H), 7.70 (m, 1H), 7.37-7.27 (m, 5H), 7.14 (m, 1H), 4.31 (m, 2H), 1.81 (s, 6H), 1.74 (m, 2H), 1.31-1.29 (m, 4H), 0.90 (m, 3H).

SGT-172



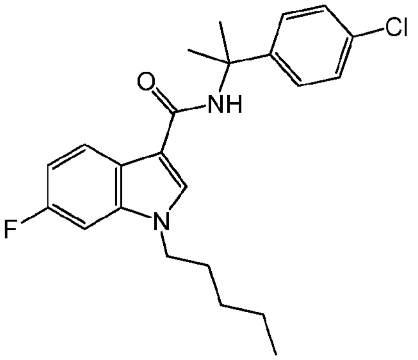
^{1}H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 8.00 (s, 1H), 7.90 (m, 1H), 7.69 (m, 1H), 7.41 (m, 2H), 7.24 (m, 2H), 7.15 (m, 1H), 4.51 (m, 2H), 1.82 (s, 6H), 1.74 (m, 2H), 1.31-1.29 (m, 4H), 0.90 (m, 3H).

SGT-173



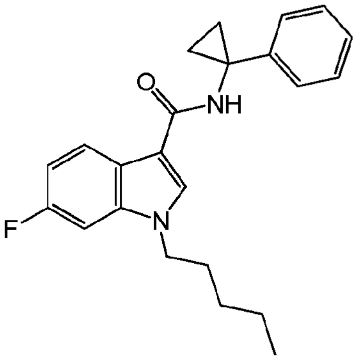
^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 8.00 (s, 1H), 7.84 (m, 1H), 7.69 (m, 1H), 7.37-7.27 (m, 5H), 7.15 (m, 1H), 4.31 (m, 2H), 1.74 (m, 2H), 1.31-1.29 (m, 4H), 0.90 (m, 3H), 0.85 (m, 2H), 0.60 (m, 2H).

SGT-182



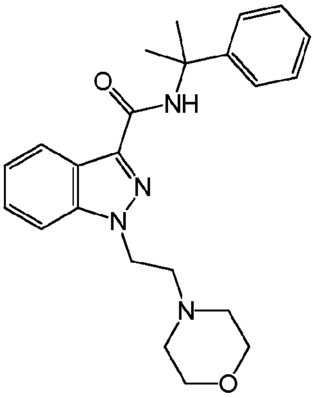
^{1}H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.90 (m, 1H), 7.41 (m, 2H), 7.31 (m, 1H), 7.24 (m, 2H), 7.15 (m, 1H), 4.51 (m, 2H), 1.82 (s, 6H), 1.74 (m, 2H), 1.31-1.29 (m, 4H), 0.90 (m, 3H).

SGT-183



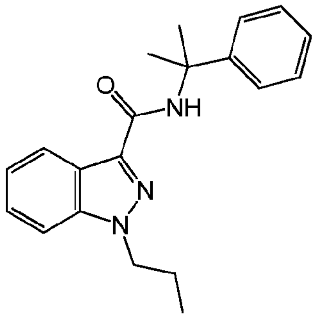
^{1}H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 7.90 (m, 1H), 7.37-7.27 (m, 6H), 7.15 (m, 1H), 4.51 (m, 2H), 1.74 (m, 2H), 1.31-1.29 (m, 4H), 0.90 (m, 3H), 0.85 (m, 2H), 0.60 (m, 2H).

SGT-184



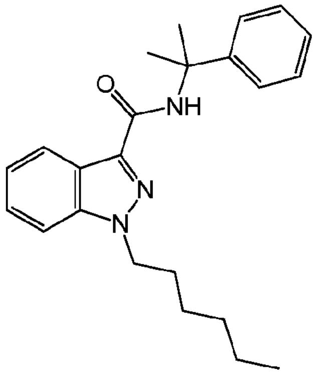
^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (m, 1H), 8.03 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.47 (m, 1H), 3.75 (m, 2H), 3.65 (m, 4H), 2.36 (m, 4H), 1.83 (s, 6H).

SGT-185



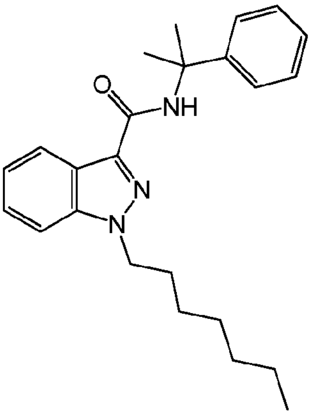
^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (m, 1H), 8.03 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.47 (m, 1H), 1.83 (s, 6H), 1.60 (m, 2H), 0.87 (m, 3H).

SGT-186



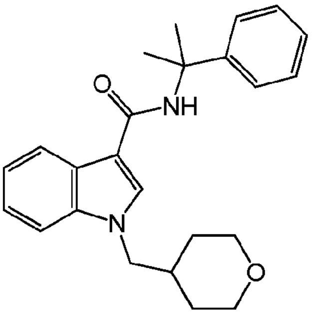
^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (m, 1H), 8.03 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.47 (m, 1H), 1.83 (s, 6H), 1.69-1.24 (m, 8H), 0.87 (m, 3H).

SGT-187



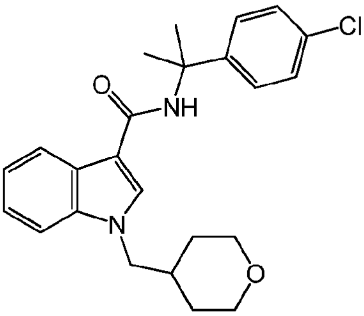
^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (m, 1H), 8.03 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.47 (m, 1H), 1.83 (s, 6H), 1.69-1.24 (m, 10H), 0.88 (m, 3H).

SGT-188



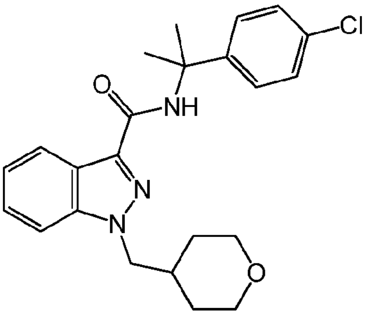
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 4.47 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 4.47 (m, 1H), 3.65-3.55 (m, 4H), 1.83 (s, 6H), 1.69-1.44 (m, 5H).

SGT-205



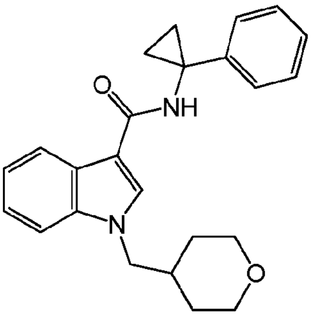
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.68 (s, 1H), 7.42 (m, 3H), 7.29 (m, 4H), 6.26 (s, 1H), 4.47 (m, 1H), 3.65-3.55 (m, 4H), 1.83 (s, 6H), 1.69-1.44 (m, 5H).

SGT-206



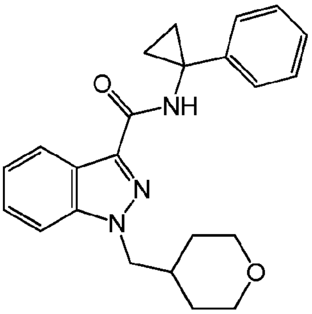
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 7.43 (m, 2H), 7.39 (m, 2H), 7.37 (s, 1H), 7.29 (m, 2H), 7.26 (s, 1H), 7.21 (m, 1H), 4.51 (m, 2H), 3.65-3.55 (m, 4H), 1.70 (s, 6H), 1.69-1.44 (m, 5H).

SGT-207



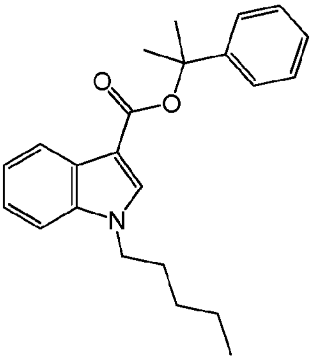
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (s, 1H), 7.66 (m, 2H), 7.40 (m, 2H), 7.38 (m, 2H), 6.26 (s, 1H), 4.51 (m, 2H), 3.65-3.55 (m, 4H), 1.69-1.44 (m, 5H), 0.85 (m, 2H), 0.60 (m, 2H).

SGT-208



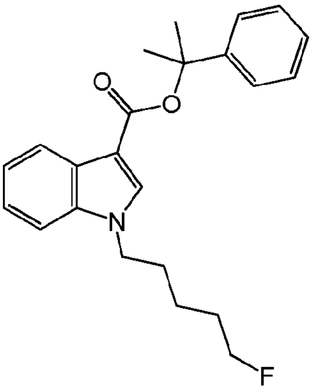
^{1}H NMR (400 MHz, DMSO-d6) δ 8.29 (m, 1H), 8.03 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4.51 (m, 2H), 3.65-3.55 (m, 4H), 1.69-1.44 (m, 5H), 0.85 (m, 2H), 0.60 (m, 2H).

SGT-209



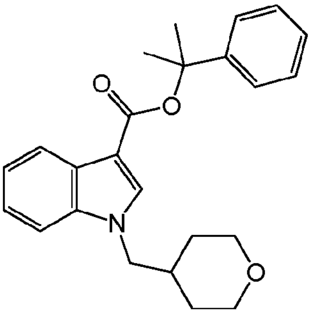
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 4.17 (m, 2H), 1.77 (m, 2H), 1.65 (s, 6H), 1.31 (m, 4H), 0.90 (m, 3H)

SGT-210



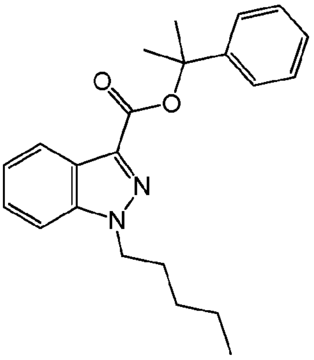
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 4,48 (m, 1H), 4.36 (m, 1H), 4.15 (m, 2H), 1.90 (m, 2H), 1.82 (s, 6H), 1.70 (m, 2H), 1.45 (m, 2H).

SGT-212



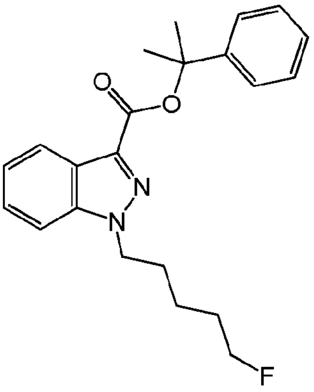
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 4,50 (m, 2H), 3.65-3.55 (m, 4H), 1.70 (s, 6H), 1.69-1.44 (m, 5H).

SGT-213



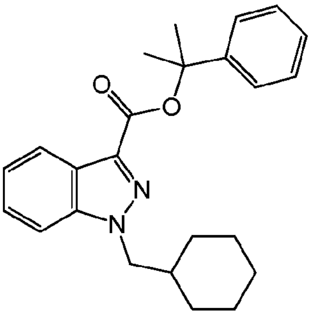
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 4.48 (m, 2H), 1.85 (m, 2H), 1.70 (s, 6H), 1.30-1.23 (m, 4H), 0.84 (m, 3H).

SGT-214



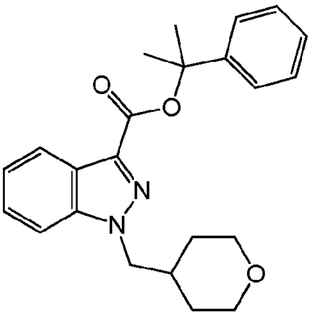
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 3H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 4,50 (m, 1H), 4.40 (m, 3H), 1.85 (m, 2H), 1.70 (s, 6H), 1.70-1.50 (m, 4H).

SGT-215



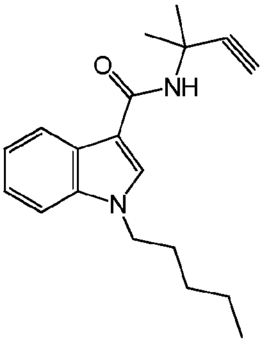
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 8.04 (s, 1H), 7.93 (m, 1H), 7.64 (m, 1H), 7.44 (m, 1H), 7.42 (m, 2H), 7.37 (m, 2H), 7.21 (m, 1H), 4,50 (m, 2H), 1.70 (s, 6H), 1.69-1.27 (m, 11H).

SGT-216



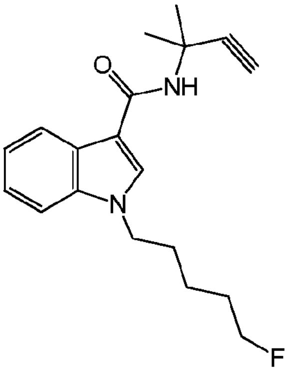
^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (m, 1H), 8.03 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 7.40 (m, 2H), 7.38 (m, 2H), 7.20 (m, 1H), 4,50 (m, 2H), 3.65-3.55 (m, 4H), 1.70 (s, 6H), 1.69-1.44 (m, 5H).

SGT-227



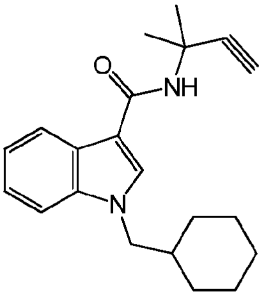
^{1}H NMR (400 MHz, DMSO-d6) δ 7.89 (m, 1H), 7.68 (s, 1H), 7.60 (s, 1H), 7.43 (m, 1H), 7.33 (m, 2H), 4,45 (m, 2H), 3.26 (s, 1H), 1.74 (m, 2H), 1.70 (s, 6H), 1.30 (m, 4H), 0.89 (m, 3H).

SGT-228



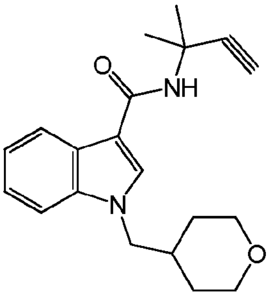
^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (m, 1H), 7.68 (s, 1H), 7.56 (s, 1H), 7.41 (m, 1H), 7.28 (m, 2H), 4.46 (m, 1H), 4.376 (m, 1H), 4.14 (m, 2H), 3.27 (s, 1H), 1,75 (m, 2H), 1.59 (s, 6H), 1.49 (m, 2H), 1.29 (m, 2H).

SGT-229



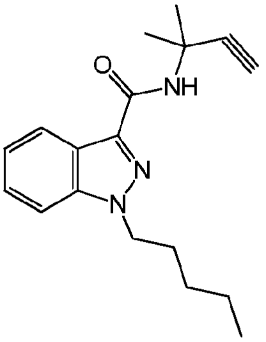
^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (m, 1H), 7.68 (s, 1H), 7.60 (s, 1H), 7.43 (m, 1H), 7.28 (m, 2H), 4.45 (m, 2H), 3.26 (s, 1H), 1.70 (s, 6H), 1.69-1.27 (m, 9H).

SGT-230



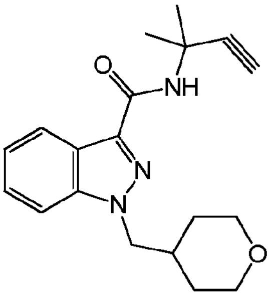
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 8.0 (s, 1H), 7.80 (s, 1H), 7.43 (m, 1H), 7.28 (m, 2H), 4,51 (m, 2H), 3.65 (m, 2H), 3.55 (m, 2H), 3.26 (s, 1H), 1.70 (s, 6H), 1.69-1.60 (m, 4H), 1.60 (m, 1H).

SGT-231



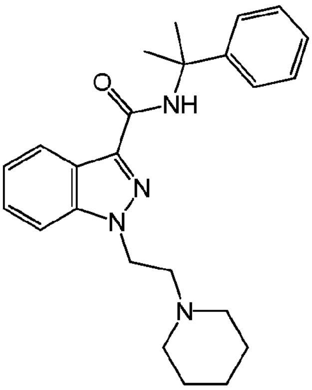
^{1}H NMR (400 MHz, DMSO-d6) δ 8.30 (m, 1H), 7.98 (s, 1H), 7.92 (m, 1H), 7.61 (m, 1H), 7.48 (m, 1H), 4.48 (m, 2H), 3.25 (s, 1H), 1.75 (m, 2H), 1.70 (s, 6H), 1.30-1.28 (m, 4H), 0.84 (m, 3H).

SGT-232



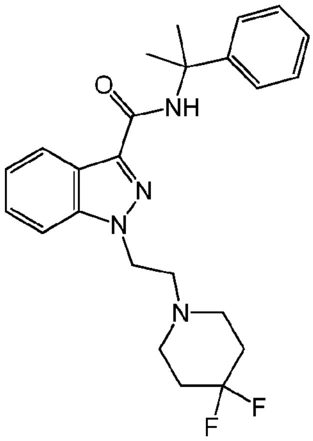
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 8.02 (s, 1H), 7.91 (m, 1H), 7.63 (m, 1H), 7.48 (m, 1H), 4,50 (m, 2H), 3.65 (m, 2H), 3.55 (m, 2H), 3.26 (s, 1H), 1.74 (m, 1H), 1.70 (s, 6H), 1.69-1.44 (m, 4H), 1.60 (m, 1H).

SGT-234



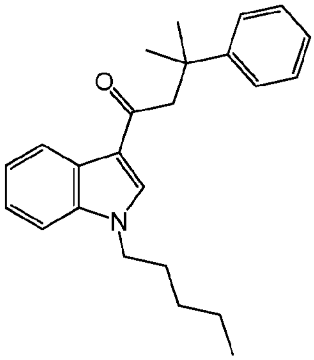
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.90 (m, 1H), 7.72 (m, 2H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 1H), 4.36 (m, 2H), 3.75 (m, 2H), 2.45 (m, 4H), 1.90 (m, 2H), 1.82 (s, 6H), 1.59-1.50(m, 6H).

SGT-235



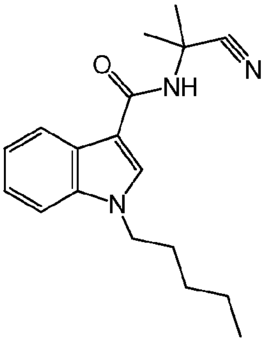
^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (m, 1H), 7.89 (m, 1H), 7.72 (m, 2H), 7.66 (s, 1H), 7.40 (m, 2H), 7.38 (m, 1H), 5.36 (m, 2H), 3.74 (m, 2H), 2.45 (m, 4H), 1.82 (s, 6H), 1.80 (m, 4H).

SGT-236



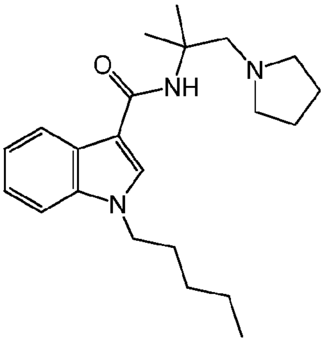
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.58 (m, 1H), 7.57-7.37 (m, 6H), 7.25 (m, 1H), 4.15 (m, 2H), 2.65 (s, 2H), 1.70 (m, 2H), 1.45 (s, 6H), 1.31 (m, 2H), 0.90 (m, 3H).

SGT-238



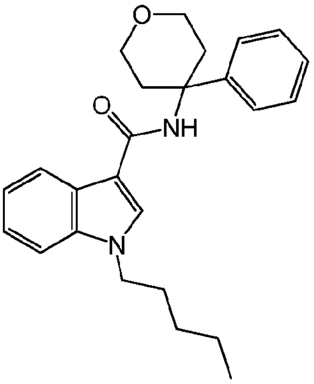
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.68 (s, 1H), 7.57 (m, 1H), 7.45 (m, 2H), 6.28 (s, 1H), 4.35 (m, 2H), 1.70 (m, 2H), 1.65 (s, 6H), 1.31 (m, 4H), 0.90 (m, 3H).

SGT-239



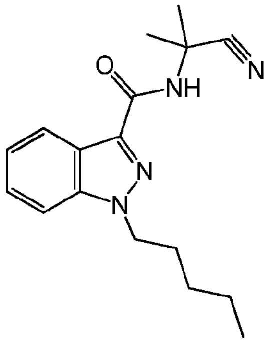
^{1}H NMR (400 MHz, DMSO-d6) δ 7.94 (m, 1H), 7.67 (s, 1H), 7.57 (m, 1H), 7.43 (m, 2H), 6.27 (s, 1H), 4.25 (m, 2H), 2.53 (m, 6H), 1.72 (m, 2H), 1.69 (m, 4H), 1.65 (s, 6H), 1.31 (m, 4H), 0.90 (m, 3H).

SGT-240



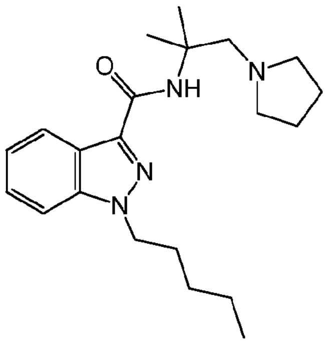
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.68 (s, 1H), 7.58 (m, 1H), 7.57-7.37 (m, 7H), 7.25 (m, 1H), 4.25 (m, 2H), 3.66 (m, 4H), 2.25 (m, 4H), 1.70 (m, 2H), 1.31 (m, 2H), 0.90 (m, 3H).

SGT-241



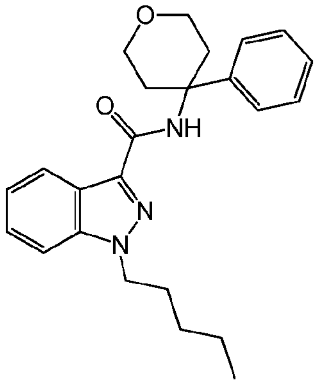
^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (m, 1H), 8.04 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 4.35 (m, 2H), 1.70 (m, 2H), 1.65 (s, 6H), 1.31 (m, 4H), 0.90 (m, 3H).

SGT-242



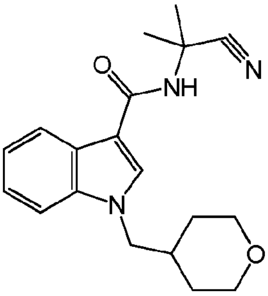
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 8.04 (s, 1H), 7.92 (m, 1H), 7.62 (m, 1H), 7.42 (m, 1H), 4.25 (m, 2H), 2.53 (m, 6H), 1.72 (m, 2H), 1.69 (m, 4H), 1.65 (s, 6H), 1.31 (m, 4H), 0.90 (m, 3H).

SGT-243



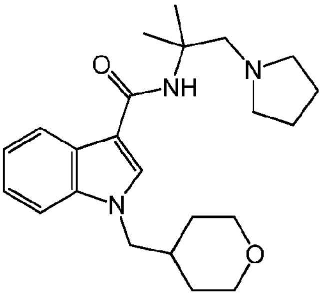
^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (m, 1H), 8.04 (s, 1H), 7.57-7.37 (m, 7H), 7.25 (m, 1H), 4.25 (m, 2H), 3.66 (m, 4H), 2.25 (m, 4H), 1.70 (m, 2H), 1.31 (m, 2H), 0.90 (m, 3H).

SGT-244



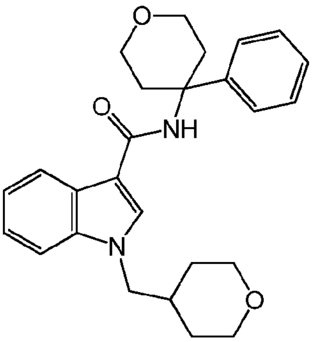
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 8.0 (s, 1H), 7.80 (s, 1H), 7.43 (m, 1H), 7.28 (m, 2H), 4.35 (m, 2H), 3.55 (m, 4H), 1.65 (s, 6H), 1.61 (m, 1H), 1.48 (m, 4H).

SGT-245



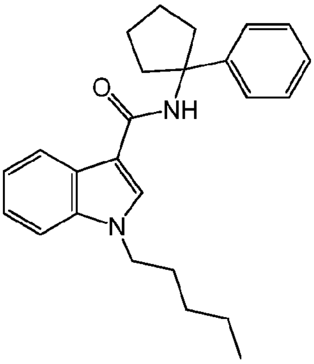
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 8.0 (s, 1H), 7.80 (s, 1H), 7.43 (m, 1H), 7.28 (m, 2H), 4.35 (m, 2H), 3.55 (m, 4H), 2.51 (m, 6H), 1.69 (m, 8H), 1.66 (s, 6H), 1.61 (m, 1H), 1.48 (m, 4H).

SGT-246



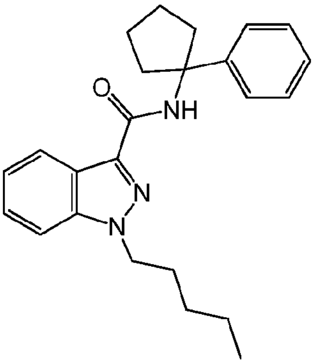
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 8.0 (s, 1H), 7.80 (s, 1H), 7.43 (m, 1H), 7.35-7.27 (m, 7H), 4.35 (m, 2H), 3.55 (m, 8H), 2.23 (m, 4H), 1.61 (m, 1H), 1.48 (m, 4H).

SGT-247



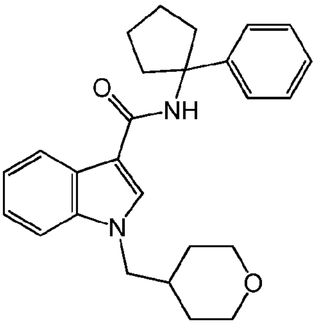
^{1}H NMR (400 MHz, DMSO-d6) δ 7.92 (m, 1H), 7.68 (s, 1H), 7.58 (m, 1H), 7.57-7.37 (m, 7H), 7.25 (m, 1H), 4.47 (m, 2H), 2.15 (m, 4H), 1.77 (m, 2H), 1.55 (m, 4H), 1.31 (m, 4H), 0.90 (m, 3H)

SGT-248



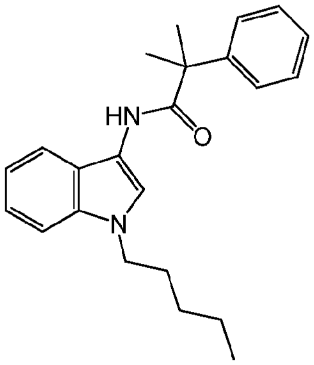
^{1}H NMR (400 MHz, DMSO-d6) δ 8.22 (s, 1H), 7.99 (dd, *J*=7.0, 1.2Hz, 1H), 7.52 (s, 1H), 7.49 (dd, *J*=7.0, 1.2Hz, 1H), 7.38 (m, 1H), 7.34 (m, 2H), 7.12 (m, 2H), 7.06 (m, 1H), 4.47 (m, 2H), 2.15 (m, 4H), 1.77 (m, 2H), 1.55 (m, 4H), 1.31 (m, 4H), 0.90 (m, 3H)

SGT-249



^{1}H NMR (400 MHz, DMSO-d6) δ 7.91 (m, 1H), 7.67 (s, 1H), 7.59 (m, 1H), 7.57-7.37 (m, 7H), 7.25 (m, 1H), 4.47 (m, 2H), 3.55 (m, 4H), 2.15 (m, 4H), 1.67 (m, 4H), 1.62 (m, 1H), 1.55 (m, 4H).

SGT-250



^{1}H NMR (400 MHz, DMSO-d6) δ 7.61 (m, 1H), 7.57-7.37 (m, 7H), 7.23 (s, 1H), 7.19 (s, 1H), 7.12 (m, 1H), 4.47 (m, 2H), 1.77 (s, 6H), 1.67 (m, 2H), 1.32 (m, 4H), 0.91 (m, 3H).

Solubility of SGT-42

The solubility of SGT-42 was tested in water, dimethyl sulfoxide, and propane-1,2-diol (propylene glycol) according to British Pharmacopoeia procedures for determining solubility. Approximately 50 mg of SGT-42 was added to each solvent. The results are summarised in Table 4 below.

Table 4.

Solvent	Solubility
Water	Not soluble in 10 mL solvent (formed agglomerates)
Dimethyl sulfoxide	Soluble in 1 mL solvent
Propane-1,2-diol (propylene glycol)	Not soluble in 10 mL solvent

6.2 Cannabinoid receptor binding affinity

The cannabinoid receptor binding affinity of selected compounds of the invention was evaluated using the following tests.

GPCR functional assay: Human cannabinoid CB1 receptor – agonist effect

This test evaluated the agonist activity of compounds of the invention at the human CB1 receptor expressed in transfected CHO cells, as determined by measuring their effects on cAMP modulation using the HTRF detection method.

The cells were suspended in HBSS buffer (Invitrogen) complemented with 20 mM HEPES (pH 7.4), then distributed in microplates at a density of 5.10^3 cells/well in the presence of either of the following: HBSS (basal control), the reference agonist at 30 nM (stimulated control) or various concentrations (EC_{50} determination), or the test compound.

Thereafter, the adenylyl cyclase activator NKH 477 was added at a final concentration of 3 μM.

Following 20 min incubation at 37°C, the cells were lysed and the fluorescence acceptor (D2-labeled cAMP) and fluorescence donor (anti-cAMP antibody labeled with europium cryptate) were added.

After 60 min at room temperature, the fluorescence transfer was measured at $\lambda ex=337$ nm and $\lambda em=620$ and 665 nm using a microplate reader (Rubystar, BMG).

The cAMP concentration was determined by dividing the signal measured at 665 nm by that measured at 620 nm (ratio).

The results are expressed as a percent of the control response to 30 nM CP 55940.

The standard reference agonist was CP 55940, which was tested in each experiment at several concentrations to generate a concentration-response curve from which its EC_{50} value was calculated.

Reference: FELDER, C.C., JOYCE, K.E., BRILET, E.M., MANSOURI, J., MACKIE, K., BLOND, O., LAI, Y., MA, A.L. and MITCHELL, R.L. (1995), Comparison of the pharmacology and signal transduction of the human cannabinoid CB_1 and CB_2 receptors, Mol. Pharmacol., 48: 443.

Assay volume and format:	20 µl in 96-well plate
Compound addition:	[100x] solution in solvent then [10x] solution in HBSS and 0.1% BSA

Maximum tolerable DMSO concentration: 1%

The results of the tests are summarised in Table 5 below.

GPCR functional assay: Human cannabinoid CB_2 receptor – agonist effect

This test evaluated the agonist activity of compounds of the invention at the human CB_2 receptor expressed in transfected CHO cells, as determined by measuring their effects on cAMP modulation using the HTRF detection method.

The cells were suspended in HBSS buffer (Invitrogen) complemented with 20 mM HEPES (pH 7.4), then distributed in microplates at a density of 7.5×10^3 cells/well in the presence of either of the following: HBSS (basal control), the reference agonist at 100 nM (stimulated control) or various concentrations (EC_{50} determination), or the test compound.

Thereafter, the adenylyl cyclase activator NKH 477 was added at a final concentration of 3 µM.

Following 10 min incubation at 37°C, the cells were lysed and the fluorescence acceptor (D2-labeled cAMP) and fluorescence donor (anti-cAMP antibody labeled with europium cryptate) were added.

After 60 min at room temperature, the fluorescence transfer was measured at $\lambda ex=337$ nm and $\lambda em=620$ and 665 nm using a microplate reader (Rubystar, BMG).

The cAMP concentration was determined by dividing the signal measured at 665 nm by that measured at 620 nm (ratio).

The results are expressed as a percent of the control response to 100 nM WIN 55212-2.

The standard reference agonist was WIN 55212-2, which was tested in each experiment at several concentrations to generate a concentration-response curve from which its EC_{50} value was calculated.

Reference: FELDER, C.C., JOYCE, K.E., BRILET, E.M., MANSOURI, J., MACKIE, K., BLOND, O., LAI, Y., MA, A.L. and MITCHELL, R.L. (1995), Comparison of the pharmacology and signal transduction of the human cannabinoid CB_1 and CB_2 receptors, Mol. Pharmacol., 48: 443.

Assay volume and format:	20 µl in 96-well plate
Compound addition:	[100x] solution in solvent then [10x] solution in HBSS and 0.1% BSA

Maximum tolerable DMSO concentration: 1%

The results of the tests are summarised in Table 5 below.

Table 5.

Compound	CB_1 EC50 (nM)	CB_2 EC50 (nM)
SGT-24	0.15	0.41
SGT-25	< 0.1 #	0.37
SGT-42	0.10	0.59
SGT-56	0.66	13
SGT-60	0.17	0.69
SGT-65	< 0.1 #	0.61
SGT-149	< 0.1 #	0.21
SGT-153	0.72	5.7
SGT-161	2.8	29
SGT-209	N.C. ##	N.C. ##
SGT-214	2200	94
SGT-238	2500	6300
SGT-239	200	440
SGT-240	3.6	11
SGT-247	10	4.7

EC50 value below the lowest test concentration. Concentration-response curve shows more than 50 % effect at the lowest validated testing concentration.
EC50 value not calculable. Concentration-response curve shows less than 25% effect at the highest validated testing concentration.

6.3 Off-target G-protein coupled receptor and ligand-gated ion channel screen

Fifteen compounds (SGT-24, SGT-25, SGT-42, SGT-56, SGT-60, SGT-65, SGT-149, SGT-153, SGT-161, SGT-209, SGT-214, SGT-238, SGT-239, SGT-240 and SGT-247) were tested at 1µM to measure their binding affinity against a panel of 53 common G-protein coupled receptor and ligand-gated ion channel targets, to assess their potential to cause side effects.

The receptors and channels tested against were adenosine A1, A2A and A3, adrenergic α1, α2, β1 and β2, angiotensin AT1, central benzodiazepine BZD, bradykinin B2, cholecystokinin CCK1, dopamine D1 and D2S, endothelin ETA, GABA (non-selective), galanin GAL2, chemokine CXCR2 and CCR1, histamine H1 and H2, melatonin MT1, muscarininc M1, M2 and M3, tachykinin NK2 and NK3, neuropeptide Y Y1 and Y2, neurotensin NTS1, opioid μ, δ, κ and NOP, prostaglandin EP4, serotonin 5-HT1A, 1B, 2A, 2B, 3, 5A, 6 and 7, somatostatin SST, vasoactive intestinal polypeptide VPAC1, vasopressin V1A, Ca2+ channel L, KV channel, SKCa channel, Na+ channel (site 2), Cl- channel (GABA-gated), noradrenaline transporter, dopamine transporter and serotonin transporter. In general, the affinity of the compounds tested at these targets was significantly lower than that recorded against the cannabinoid CB1 and CB2 receptors.

Only two target – ligand combinations achieved more than 50% displacement of the appropriate reference ligand at 1µM. SGT-153 achieved 53% displacement of IB-MECA from adenosine A3 receptor at 1µM and SGT-60 achieved 60% displacement of diazepam from central benzodiazepine receptor at 1µM.

Some weak affinity was seen against 5-HT1A and MT1 receptors. However, due to their high CB1 and CB2 affinity, the tested compounds are still generally highly selective for CB1 and CB2 receptors.

The data in Table 6 shows that the Ki of compounds SGT-24, SGT-25, SGT-42, SGT-60, SGT-65 and SGT-149 is greater than 1000 nM. The data in Table 5 shows that the EC50 for these compounds is less than 1 nM. This suggests that these compounds were over 1,000x selective for CB1 and CB2 receptors over all other receptors and channels tested, and that compound SGT-42 was close to 10,000x selectivite for CB1 and CB2.

The results of the assay screen for SGT-24, SGT-42, SGT-65 and SGT-149 are provided in Table 6 below (each assay is in bold, followed by the reference radioligand used in that assay).

Most of the compounds were selective for CB1 over CB2. SGT-56 the highest selectivity, being 19.7x selective for CB1 over CB2.

SGT-214, by contrast was 23.4x selective for CB2 over CB1.

Table 6.

Test compound and reference compound concentration (M): 1.0E-06					
Compound	% Inhibition of Control Specific Binding	% of Control Specific Binding (mean)	IC50 Ref (M)	Ki Ref (M)	nH Ref
A1 (h) (antagonist radioligand)			DPCPX		
SGT-24	-13	113.0	1.1E-09	7.2E-10	1.2
SGT-42	-8	108.1	1.1E-09	7.2E-10	1.2
SGT-65	-4	103.9	1.1E-09	7.2E-10	1.2
SGT-149	-7	106.9	1.1E-09	7.2E-10	1.2
A2A (h) (agonist radioligand)			NECA		
SGT-24	9	90.7	1.8E-08	1.5E-08	0.9
SGT-42	3	97.4	1.8E-08	1.5E-08	0.9
SGT-65	-5	105.4	1.8E-08	1.5E-08	0.9
SGT-149	5	95.1	1.8E-08	1.5E-08	0.9
A3 (h) (agonist radioligand)			IB-MECA		
SGT-24	11	89.1	2.3E-10	1.4E-10	0.7
SGT-42	-9	108.5	2.3E-10	1.4E-10	0.7
SGT-65	5	95.4	2.3E-10	1.4E-10	0.7
SGT-149	22	78.3	2.3E-10	1.4E-10	0.7
alpha 1 (non-selective) (antagonist radioligand)			prazosin		
SGT-24	-3	103.1	1.6E-10	4.1E-11	0.9

SGT-42	-3	103.2	1.6E-10	4.1E-11	0.9
SGT-65	-6	106.2	1.6E-10	4.1E-11	0.9
SGT-149	-6	105.9	1.6E-10	4.1E-11	0.9
alpha 2 (non-selective) (antagonist radioligand)			yohimbine		
SGT-24	-4	103.5	3.9E-08	1.7E-08	0.8
SGT-42	-14	113.8	3.9E-08	1.7E-08	0.8
SGT-65	-17	116.7	3.9E-08	1.7E-08	0.8
SGT-149	-8	108.0	3.9E-08	1.7E-08	0.8
beta 1 (h) (agonist radioligand)			atenolol		
SGT-24	0	99.8	2.3E-07	1.3E-07	0.9
SGT-42	8	92.1	2.3E-07	1.3E-07	0.9
SGT-65	3	97.4	2.3E-07	1.3E-07	0.9
SGT-149	-2	102.3	2.3E-07	1.3E-07	0.9
beta 2 (h) (agonist radioligand)			ICI 118551		
SGT-24	-1	100.7	7.2E-10	2.4E-10	1.2
SGT-42	1	98.6	7.2E-10	2.4E-10	1.2
SGT-65	0	100.2	7.2E-10	2.4E-10	1.2
SGT-149	-4	103.8	7.2E-10	2.4E-10	1.2
AT1 (h) (antagonist radioligand)			saralasin		
SGT-24	-14	113.8	4.5E-10	2.2E-10	0.8
SGT-42	6	94.4	4.5E-10	2.2E-10	0.8
SGT-65	9	90.6	4.5E-10	2.2E-10	0.8
SGT-149	1	98.7	4.5E-10	2.2E-10	0.8
BZD (central) (agonist radioligand)			diazepam		
SGT-24	-45	144.6	6.5E-09	5.5E-09	0.8
SGT-42	-25	125.1	6.5E-09	5.5E-09	0.8
SGT-65	-42	141.9	6.5E-09	5.5E-09	0.8
SGT-149	-41	140.6	6.5E-09	5.5E-09	0.8
B2 (h) (agonist radioligand)			NPC 567		
SGT-24	-7	106.7	2.7E-08	1.4E-08	0.8
SGT-42	-3	102.6	2.7E-08	1.4E-08	0.8
SGT-65	-5	104.8	2.7E-08	1.4E-08	0.8
SGT-149	0	100.3	2.7E-08	1.4E-08	0.8
CB1 (h) (agonist radioligand)			CP 55940		
SGT-24	105	-4.7	6.6E-10	5.8E-10	1.0
SGT-42	100	-0.4	6.6E-10	5.8E-10	1.0
SGT-65	103	-2.5	6.6E-10	5.8E-10	1.0
SGT-149	99	0.8	6.6E-10	5.8E-10	1.0
CCK1 (CCKA) (h) (agonist radioligand)			CCK-8s		
SGT-24	-11	110.7	8.8E-11	6.6E-11	1.4
SGT-42	-9	109.5	8.8E-11	6.6E-11	1.4
SGT-65	2	97.9	8.8E-11	6.6E-11	1.4

SGT-149	-41	141.3	8.8E-11	6.6E-11	1.4
D1 (h) (antagonist radioligand)			SCH 23390		
SGT-24	-1	101.4	2.7E-10	1.1E-10	1.2
SGT-42	10	90.1	2.7E-10	1.1E-10	1.2
SGT-65	9	90.9	2.7E-10	1.1E-10	1.2
SGT-149	14	86.1	2.7E-10	1.1E-10	1.2
D2S (h) (antagonist radioligand)			(+)butaclamol		
SGT-24	9	90.8	2.8E-09	9.5E-10	1.1
SGT-42	9	90.9	2.8E-09	9.5E-10	1.1
SGT-65	-4	104.3	2.8E-09	9.5E-10	1.1
SGT-149	13	87.3	2.8E-09	9.5E-10	1.1
ETA (h) (agonist radioligand)			endothelin-1		
SGT-24	-3	102.7	3.0E-11	1.5E-11	0.8
SGT-42	8	92.5	3.0E-11	1.5E-11	0.8
SGT-65	-3	102.6	3.0E-11	1.5E-11	0.8
SGT-149	-2	102.4	3.0E-11	1.5E-11	0.8
GABA (non-selective) (agonist radioligand)			GABA		
SGT-24	-3	103.5	6.7E-08	4.0E-08	1.0
SGT-42	-1	100.9	6.7E-08	4.0E-08	1.0
SGT-65	0	99.5	6.7E-08	4.0E-08	1.0
SGT-149	-12	111.9	6.7E-08	4.0E-08	1.0
GAL2 (h) (agonist radioligand)			galanin		
SGT-24	-5	104.8	2.8E-10	2.6E-10	0.9
SGT-42	-5	105.0	2.8E-10	2.6E-10	0.9
SGT-65	-5	104.8	2.8E-10	2.6E-10	0.9
SGT-149	-12	111.5	2.8E-10	2.6E-10	0.9
CXCR2 (IL-8B) (h) (agonist radioligand)			IL-8		
SGT-24	-14	114.2	2.3E-10	1.1E-10	1.5
SGT-42	-13	113.2	2.3E-10	1.1E-10	1.5
SGT-65	-12	111.9	2.3E-10	1.1E-10	1.5
SGT-149	-1	101.3	2.3E-10	1.1E-10	1.5
CCR1 (h) (agonist radioligand)			MIP-1alpha		
SGT-24	-4	104.1	8.3E-11	5.5E-11	1.3
SGT-42	-4	103.7	8.3E-11	5.5E-11	1.3
SGT-65	-14	114.1	8.3E-11	5.5E-11	1.3
SGT-149	-7	107.4	8.3E-11	5.5E-11	1.3
H1 (h) (antagonist radioligand)			pyrilamine		
SGT-24	-16	115.5	2.4E-09	1.5E-09	1.2
SGT-42	-19	118.6	2.4E-09	1.5E-09	1.2
SGT-65	-5	104.8	2.4E-09	1.5E-09	1.2

SGT-149	-12	111.8	2.4E-09	1.5E-09	1.2
H2 (h) (antagonist radioligand)			cimetidine		
SGT-24	0	100.0	4.5E-07	4.3E-07	1.1
SGT-42	-5	104.8	4.5E-07	4.3E-07	1.1
SGT-65	-18	118.2	4.5E-07	4.3E-07	1.1
SGT-149	1	99.4	4.7E-07	4.5E-07	0.7
MT1 (ML1A) (h) (agonist radioligand)			melatonin		
SGT-24	9	91.0	5.5E-10	4.4E-10	0.9
SGT-42	13	86.8	5.5E-10	4.4E-10	0.9
SGT-65	39	60.8	5.5E-10	4.4E-10	0.9
SGT-149	19	80.7	5.5E-10	4.4E-10	0.9
M1 (h) (antagonist radioligand)			pirenzepine		
SGT-24	-13	113.5	2.3E-08	2.0E-08	1.1
SGT-42	-20	120.0	2.3E-08	2.0E-08	1.1
SGT-65	-15	115.3	2.3E-08	2.0E-08	1.1
SGT-149	-21	121.4	2.3E-08	2.0E-08	1.1
M2 (h) (antagonist radioligand)			methoctramine		
SGT-24	-9	109.5	3.1E-08	2.1E-08	1.1
SGT-42	-5	105.5	3.1E-08	2.1E-08	1.1
SGT-65	-4	104.4	3.1E-08	2.1E-08	1.1
SGT-149	-4	103.8	3.1E-08	2.1E-08	1.1
M3 (h) (antagonist radioligand)			4-DAMP		
SGT-24	1	99.3	6.0E-10	4.3E-10	0.9
SGT-42	-2	102.0	6.0E-10	4.3E-10	0.9
SGT-65	0	100.1	6.0E-10	4.3E-10	0.9
SGT-149	-10	110.4	6.0E-10	4.3E-10	0.9
NK2 (h) (agonist radioligand)			[Nleu10]-NKA (4-10)		
SGT-24	-4	103.9	4.2E-09	2.3E-09	0.8
SGT-42	-7	106.9	4.3E-09	2.3E-09	0.8
SGT-65	10	90.3	4.3E-09	2.3E-09	0.8
SGT-149	4	96.3	4.3E-09	2.3E-09	0.8
NK3 (h) (antagonist radioligand)			SB 222200		
SGT-24	-8	107.8	5.5E-09	2.9E-09	0.8
SGT-42	-4	104.1	5.5E-09	2.9E-09	0.8
SGT-65	-6	106.2	5.5E-09	2.9E-09	0.8
SGT-149	-3	103.5	5.5E-09	2.9E-09	0.8
Y1 (h) (agonist radioligand)			NPY		
SGT-24	-17	117.1	8.4E-11	5.9E-11	1.0
SGT-42	-26	125.9	8.4E-11	5.9E-11	1.0
SGT-65	-12	112.1	8.4E-11	5.9E-11	1.0

SGT-149	-13	113.4	8.4E-11	5.9E-11	1.0
Y2 (h) (agonist radioligand)			NPY		
SGT-24	1	98.5	2.7E-11	1.1E-11	0.7
SGT-42	6	94.5	2.7E-11	1.1E-11	0.7
SGT-65	12	87.7	2.7E-11	1.1E-11	0.7
SGT-149	15	85.5	2.7E-11	1.1E-11	0.7
NTS1 (NT1) (h) (agonist radioligand)			neurotensin		
SGT-24	-22	122.0	2.5E-10	2.0E-10	0.7
SGT-42	-21	121.3	2.5E-10	2.0E-10	0.7
SGT-65	-28	127.6	2.5E-10	2.0E-10	0.7
SGT-149	-10	109.8	2.5E-10	2.0E-10	0.7
delta 2 (DOP) (h) (agonist radioligand)			DPDPE		
SGT-24	6	94.4	3.7E-09	2.2E-09	1.1
SGT-42	4	96.4	3.7E-09	2.2E-09	1.1
SGT-65	3	97.5	3.7E-09	2.2E-09	1.1
SGT-149	12	87.5	3.7E-09	2.2E-09	1.1
kappa (KOP) (agonist radioligand)			U 50488		
SGT-24	-4	103.9	9.4E-10	6.2E-10	1.1
SGT-42	5	95.2	9.4E-10	6.2E-10	1.1
SGT-65	0	99.7	9.4E-10	6.2E-10	1.1
SGT-149	36	64.1	9.4E-10	6.2E-10	1.1
mu (MOP) (h) (agonist radioligand)			DAMGO		
SGT-24	1	99.0	9.8E-10	4.1E-10	1.1
SGT-42	9	90.6	9.8E-10	4.1E-10	1.1
SGT-65	-4	104.3	9.8E-10	4.1E-10	1.1
SGT-149	-6	105.5	1.1E-09	4.4E-10	0.9
NOP (ORL1) (h) (agonist radioligand)			nociceptin		
SGT-24	7	93.2	8.7E-10	1.7E-10	1.4
SGT-42	8	91.9	8.7E-10	1.7E-10	1.4
SGT-65	-8	107.7	8.7E-10	1.7E-10	1.4
SGT-149	-6	105.9	8.7E-10	1.7E-10	1.4
EP4 (h) (agonist radioligand)			PGE2		
SGT-24	10	89.7	4.4E-10	1.7E-10	0.8
SGT-42	2	98.3	4.4E-10	1.7E-10	0.8
SGT-65	4	96.0	4.4E-10	1.7E-10	0.8
SGT-149	4	95.6	4.4E-10	1.7E-10	0.8
5-HT1A (h) (agonist radioligand)			8-OH-DPAT		
SGT-24	15	85.5	6.0E-10	3.7E-10	1.4
SGT-42	23	76.6	6.0E-10	3.7E-10	1.4
SGT-65	6	93.8	6.0E-10	3.7E-10	1.4
SGT-149	12	88.4	6.0E-10	3.7E-10	1.4
5-HT1B (antagonist radioligand)			serotonin		
SGT-24	-6	105.6	6.6E-09	4.1E-09	0.7

SGT-42	-3	103.4	6.6E-09	4.1E-09	0.7
SGT-65	-6	105.8	6.6E-09	4.1E-09	0.7
SGT-149	-9	108.5	6.6E-09	4.1E-09	0.7
5-HT2A (h) (antagonist radioligand)			ketanserin		
SGT-24	1	99.2	1.3E-09	6.9E-10	1.1
SGT-42	2	98.3	1.3E-09	6.9E-10	1.1
SGT-65	-4	103.8	1.3E-09	6.9E-10	1.1
SGT-149	9	90.5	1.3E-09	6.9E-10	1.1
5-HT2B (h) (agonist radioligand)			(±)DOI		
SGT-24	-8	107.6	2.5E-09	1.2E-09	1.0
SGT-42	-18	117.8	2.5E-09	1.2E-09	1.0
SGT-65	4	95.6	2.5E-09	1.2E-09	1.0
SGT-149	11	88.5	2.5E-09	1.2E-09	1.0
5-HT3 (h) (antagonist radioligand)			MDL 72222		
SGT-24	1	99.0	1.4E-08	9.6E-09	1.2
SGT-42	-6	105.9	1.4E-08	9.6E-09	1.2
SGT-65	-3	103.0	1.4E-08	9.6E-09	1.2
SGT-149	-1	100.9	1.4E-08	9.6E-09	1.2
5-HT5a (h) (agonist radioligand)			serotonin		
SGT-24	-3	103.0	1.6E-07	8.0E-08	0.8
SGT-42	-1	101.2	1.6E-07	8.0E-08	0.8
SGT-65	1	99.4	1.6E-07	8.0E-08	0.8
SGT-149	-11	110.6	1.6E-07	8.0E-08	0.8
5-HT6 (h) (agonist radioligand)			serotonin		
SGT-24	-9	108.7	9.4E-08	4.5E-08	0.9
SGT-42	-3	103.3	9.4E-08	4.5E-08	0.9
SGT-65	-5	104.5	9.4E-08	4.5E-08	0.9
SGT-149	-4	104.1	9.4E-08	4.5E-08	0.9
5-HT7 (h) (agonist radioligand)			serotonin		
SGT-24	5	95.5	4.5E-10	1.6E-10	1.1
SGT-42	7	93.0	4.5E-10	1.6E-10	1.1
SGT-65	-13	113.1	4.5E-10	1.6E-10	1.1
SGT-149	2	97.7	4.5E-10	1.6E-10	1.1
sst (non-selective) (agonist radioligand)			somatostatin-14		
SGT-24	-8	108.1	3.4E-10	2.1E-10	1.0
SGT-42	-11	110.5	3.4E-10	2.1E-10	1.0
SGT-65	-25	124.8	3.4E-10	2.1E-10	1.0
SGT-149	-26	125.7	3.4E-10	2.1E-10	1.0
VPAC1 (VIP1) (h) (agonist radioligand)			VIP		
SGT-24	-2	102.3	2.4E-10	1.3E-10	0.9

SGT-42	-3	103.4	2.4E-10	1.3E-10	0.9
SGT-65	-1	101.2	2.4E-10	1.3E-10	0.9
SGT-149	-5	104.9	2.4E-10	1.3E-10	0.9
V1a (h) (agonist radioligand)			[d(CH2)51,Tyr(Me)2]-AVP		
SGT-24	-4	104.2	7.6E-10	4.8E-10	0.9
SGT-42	5	94.5	7.6E-10	4.8E-10	0.9
SGT-65	1	98.5	7.6E-10	4.8E-10	0.9
SGT-149	-4	104.4	7.6E-10	4.8E-10	0.9
Ca2+ channel (L, verapamil site) (phenylalkylamine) (antagonist radioligand)			D 600		
SGT-24	-8	108.5	1.4E-08	7.0E-09	0.5
SGT-42	-4	103.8	1.4E-08	7.0E-09	0.5
SGT-65	-12	111.8	1.4E-08	7.0E-09	0.5
SGT-149	-7	107.5	1.4E-08	7.0E-09	0.5
KV channel (antagonist radioligand)			alpha -dendrotoxin		
SGT-24	-15	115.1	2.0E-10	1.6E-10	0.9
SGT-42	-12	111.8	2.0E-10	1.6E-10	0.9
SGT-65	-9	108.7	2.0E-10	1.6E-10	0.9
SGT-149	-4	104.1	2.0E-10	1.6E-10	0.9
SKCa channel (antagonist radioligand)			apamin		
SGT-24	1	99.2	8.5E-12	4.3E-12	0.8
SGT-42	-15	114.8	8.5E-12	4.3E-12	0.8
SGT-65	5	94.9	8.5E-12	4.3E-12	0.8
SGT-149	1	99.2	8.5E-12	4.3E-12	0.8
Na+ channel (site 2) (antagonist radioligand)			veratridine		
SGT-24	-8	108.1	8.6E-06	7.7E-06	1.3
SGT-42	6	94.4	8.6E-06	7.7E-06	1.3
SGT-65	-10	110.2	8.6E-06	7.7E-06	1.3
SGT-149	1	98.9	8.6E-06	7.7E-06	1.3
Cl- channel (GABA-gated) (antagonist radioligand)			picrotoxinin		
SGT-24	45	55.1	1.4E-07	1.2E-07	0.8
SGT-42	4	96.5	1.4E-07	1.2E-07	0.8
SGT-65	47	53.3	1.4E-07	1.2E-07	0.8
SGT-149	28	71.5	1.4E-07	1.2E-07	0.8
norepinephrine transporter (h) (antagonist radioligand)			protriptyline		
SGT-24	0	99.9	3.1E-09	2.3E-09	1.0
SGT-42	-7	107.0	3.1E-09	2.3E-09	1.0
SGT-65	-4	104.4	3.1E-09	2.3E-09	1.0
SGT-149	-1	100.8	3.1E-09	2.3E-09	1.0
dopamine transporter (h) (antagonist radioligand)			BTCP		
SGT-24	-6	105.7	9.7E-09	5.1E-09	1.1

SGT-42	-11	110.6	9.7E-09	5.1E-09	1.1
SGT-65	-1	100.6	9.7E-09	5.1E-09	1.1
SGT-149	12	88.5	9.7E-09	5.1E-09	1.1
5-HT transporter (h) (antagonist radioligand)			imipramine		
SGT-24	-7	107.5	1.9E-09	8.9E-10	0.8
SGT-42	-7	107.0	1.9E-09	8.9E-10	0.8
SGT-65	-8	108.4	1.9E-09	8.9E-10	0.8
SGT-149	3	97.1	1.9E-09	8.9E-10	0.8

6.4 Pharmaceutical compositions

Pharmaceutical compositions of the invention were prepared by dissolving a compound of the invention in a solvent, such as diethyl ether or acetone or a mixture thereof, and mixing the solution with a suitable carrier. The solvent was removed and the mixture divided up into gel caps (capsules) in equal portions so that each gel cap contained a known dose of the compound of the invention.

SGT-24 with mannitol (capsule 1)

Gel caps containing 4 mg of SGT-24 and ~196 mg mannitol as carrier were prepared as described above. 40 mg of SGT-42 was dissolved in 20 ml of diethyl ether and 1960 mg of mannitol. The mixture was dried and 200 mg of the mixture was placed in each gel cap.

SGT-24 with MSM (capsule 2)

Gel caps containing 4 mg of SGT-24 and ~196 mg methylsulfonylmethane (MSM) as carrier were prepared as described above. 40 mg of SGT-42 was dissolved in 20 ml of diethyl ether (or 20 ml of 2:1 diethyl ether: acetone) and 1960 mg of MSM. The mixture was dried and 200 mg of the mixture was placed in each gel cap.

SGT-42 with MSM (capsule 3)

Gel caps containing 5 mg of SGT-42 and ~196 mg methylsulfonylmethane (MSM) as carrier were prepared as described above. 50 mg of SGT-42 was dissolved in 20 ml of diethyl ether and 1950 mg of MSM. The mixture was dried and 200 mg of the mixture was placed in each gel cap.

6.5 E-liquid composition

E-liquid compositions of the invention for use in e-cigarettes were prepared by dissolving a compound of the invention in a solvent, such as propylene glycol, glycerine, and optionally a surfactant with stirring. Optionally, a flavour enhancer may also be added. The composition may also be filtered before use.

SGT-42 e-liquid composition (E-liquid 1)

An e-liquid containing 350mg of SGT-42 was prepared with 10 ml propylene glycol, 3 ml vegetable glycerin, 2 drops of Tween 20, and 10 drops of Tasty Puff flavour enhancer were prepared as described above. The mixture was filtered through glass wool and was then used to fill 2 ml e-cigarette cartridges.

SGT-42 tablets

A batch of tablets containing SGT-42, beta cyclodextrin, microcrystalline cellulose, magnesium stearate, and magnesium silicate in tablet form was produced as described below. The content of each component by weight is listed in Table 7.

Table 7.

Component	Weight (mg)
SGT-42	1
Beta Cyclodextrin (Cavasol W7 HP)	49
Microcrystalline Cellulose (Avicel PH101)	430
Magnesium Stearate	25
Magnesium Silicate (Talc)	25
Crosscarmellose Sodium (Vivasol)	20
Total	**550**

The cyclodextrin was weighed and placed in a ribbon blender. The SGT-42 active was weighed and fine sieved in to the ribbon blender. The ingredients were then blended for ten minutes.

The Microcrystalline Cellulose, Magnesium Silicate, and Crosscarmellose Sodium were then weighed, added to the blender, and the mixture was blended for a further ten minutes. Finally, the Magnesium Sterate was weighed, added to the mix, and blended for 5 minutes.

The blended mixture of ingredients was then tabletted.

6.6 Use of cannabinoid compounds of the invention

Capsule 1
One volunteer initially took one “capsule 1” orally.

Effects were first observed after approximately 180 minutes. The volunteer experienced strong cannabinomimetic effects. The test was not continued beyond 180 minutes.

Capsule 2
Six volunteers were breath tested to ensure they had not consumed alcohol. The volunteers were each fed a three course meal before commencement of the test. Blood pressure and heart rate of the volunteers were measured and monitored for the duration of the test.

One “capsule 2” was provided per volunteer, which was swallowed. The volunteers were asked questions every 60 minutes regarding how they were feeling and what effects they were observing.

Surprisingly, effects were first observed after approximately 20-60 minutes (when compared to 180 minutes when mannitol was used as carrier). All volunteers experienced strong cannabinomimetic effects, were relaxed, and reported a positive mood change. After a further 60 minutes, all volunteers reported that the cannabinomimetic effects had intensified and that they felt more relaxed and had an increased positive mood.

The test concluded after a further 60 minutes (180 minutes in total). The cannabinomimetic effects persisted after the test concluded.

After approximately 90 minutes, all volunteers reported experiencing voracious hunger.

None of the volunteers experienced a significant increase in blood pressure and only one volunteer experienced a significant increase in heart rate.

Capsule 3

Four volunteers were breath tested to ensure they had not consumed alcohol. Blood pressure and heart rate of the volunteers were measured and monitored for the duration of the test.

One "capsule 3" was provided per volunteer, which was swallowed. The volunteers were asked questions every 30 minutes regarding how they were feeling and what effects they were observing.

Surprisingly, effects were first observed after approximately 30 minutes (when compared to 180 minutes when mannitol was used as carrier). All volunteers experienced strong cannabinomimetic effects, were relaxed, and reported a positive mood change.

After 60 minutes, three volunteers were provided with a second "capsule 3", which was swallowed. All three volunteers reported that the cannabinomimetic effects had intensified and that they felt more relaxed and had an increased positive mood.

After 110 minutes, two of the volunteers were provided with a third "capsule 3", which was swallowed. Both volunteers reported that the cannabinomimetic effects had intensified and that they felt more relaxed and had an increased positive mood.

The test concluded after 180 minutes. The cannabinomimetic effects persisted after the test concluded.

After approximately 100 minutes, all volunteers reported experiencing voracious hunger.

None of the volunteers experienced a significant increase in blood pressure and only one volunteer experienced a significant increase in heart rate.

E-liquid 1

Five volunteers were breath tested to ensure they had not consumed alcohol. Blood pressure and heart rate of the volunteers were measured and monitored for the duration of the test.

Each volunteer was allowed to inhale two puffs of e-liquid from an e-cigarette. The volunteers were asked questions every 30 minutes regarding how they were feeling and what effects they were observing.

Effects were first observed after approximately 1-2 minutes. All volunteers experienced mild to moderate cannabinomimetic effects, were relaxed, and reported a positive mood change.

After 30 minutes most volunteers reported that the cannabinomimetic effects were diminishing, but two volunteers reported feeling cannabinomimetic effects for up to 60 minutes.

At 60 minutes the volunteers were allowed to inhale two further puffs of e-liquid from an e-cigarette. Most volunteers inhaled three or four puffs of e-liquid from the e-cigarette. All volunteers reported moderate cannabinomimetic effects at three puffs and strong cannabinomimetic effects after four puffs.

All volunteers reported cannabinomimetic effects diminishing after approximately 40 minutes after inhalation and all volunteers reported feeling no cannabinomimetic effects after 90 minutes after inhalation.

All volunteers reported feeling more relaxed and had an increased positive mood. All volunteers reported experiencing voracious hunger.

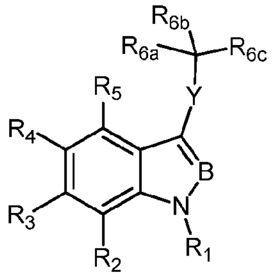
It is not the intention to limit the scope of the invention to the abovementioned examples only. As would be appreciated by a skilled person in the art, many variations are possible without departing from the scope of the invention.

7. INDUSTRIAL APPLICATION

The compounds of the invention described herein have central nervous system activity and can, therefore, be used to treat a variety of diseases or conditions. The compounds are especially useful treating pain, treating nausea and/or emesis, stimulating appetite, inducing a euphoric effect, inducing relaxation, and inducing a positive mood change, in particular for treating pain, treating nausea and/or emesis, and stimulating appetite.

CLAIMS

1. A compound of formula I,



I

wherein

Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, (C=S)NH, SCH_2, OCH_2, CH_2SO_2, OSO_2, $NHSO_2$,O(C=O), O(C=S), S(C=O), CH_2(C=O), CH_2(C=S), CH_2(C=SO_2), O(C=SO_2), NH(C=SO_2), NH(C=O), or NH(C=S);

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted;

R_2-R_5 are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or a 3 to 7 membered heterocyclyl ring; and

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, heteroaryl, or cyano, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl which may be optionally substituted; or

a pharmaceutically acceptable salt or prodrug thereof.

2. The compound of claim 1, wherein

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring; and

R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted.

3. The compound of claim 1, wherein R_{6a} and R_{6b} together form 3 to 7 membered heterocycle.

4. The compound of claim 1 wherein R_{6c} is cyano.

5. The compound of any one of claims 1 to 4, wherein Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, or (C=S)NH.

6. The compound of any one of claims 1 to 4, wherein Y is selected from CH_2CH_2, CH_2S, CH_2O, SO_2CH_2, SO_2O, SO_2NH, (C=O)O, (C=S)O, (C=O)S, (C=O)CH_2, (C=S)CH_2, (C=SO_2)CH_2, (C=SO_2)O, (C=SO_2)NH, (C=O)NH, (C=S)NH, CH_2(C=O), O(C=O), CH_2(C=O), or NH(C=O).

7. The compound of any one of claims 1 to 4, wherein Y is selected from (C=O)O, (C=O)CH_2, (C=O)NH, or NH(C=O).

8. The compound of any one of claims 1 to 4, wherein Y is selected from (C=O)O or (C=O)NH.

9. The compound of any one of claims 1 to 4, wherein Y is (C=O)NH.

10. The compound of any one of claims 1 to 9, wherein R_2-R_5 are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

11. The compound of any one of claims 1 to 10, wherein R_2-R_5 are each independently selected from hydrogen or halo.

12. The compound of any one of claims 1 to 11, wherein R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, C_6-C_{12} heteroaryl, or cyano, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

13. The compound of any one of claims 1 to 12, wherein R_{6c} is selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 haloalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12}

heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, aryl, haloaryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, -$P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

14. The compound of any one of claims 1 to 12, wherein R_{6c} is selected from C_1-C_8 alkylene heterocyclyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, or cyano, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, -$OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

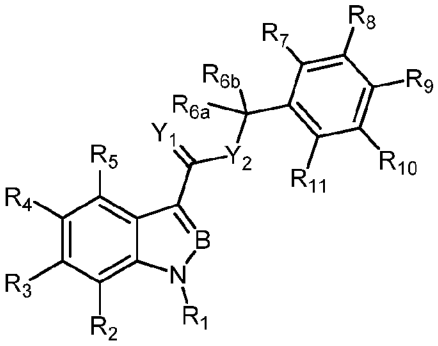
wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

15. The compound of any one of claims 1 to 12, wherein R_{6c} is selected from C_1-C_8 alkylene heterocyclyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_6-C_{12} haloaryl, or cyano, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more halo.

16. The compound of any one of claims 1 to 12, wherein R_{6c} is selected from C_1-C_8 alkylene heterocyclyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, or C_6-C_{12} haloaryl, wherein each of said heterocyclyl, alkynyl, aryl, or haloaryl may be optionally substituted by one or more halo.

17. A compound of formula Ia,



Ia

wherein

Y_1 is selected from O, S, or SO_2;

Y_2 is selected from CH_2, O, or NH;

B is selected from CH or N;

R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, aryl, cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted;

R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted;

R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or 3 to 7 membered heterocyclyl ring; and

R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted; or

a pharmaceutically acceptable salt or prodrug thereof.

18. The compound of claim 17, wherein R_{6a} and R_{6b} are each independently selected from C_1-C_8 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring.

19. The compound of claim 17, wherein R_{6a} and R_{6b} together form 3 to 7 membered heterocycle.

20. The compound of any one of claims 17 to 19, wherein Y_1 is selected from O, S, or SO_2.

21. The compound of any one of claims 17 to 20, wherein Y_1 is O.

22. The compound of any one of claims 17 to 21, wherein Y_2 is selected from CH_2, O, or NH.

23. The compound of any one of claims 17 to 22, wherein Y_2 is selected from NH or O.

24. The compound of any one of claims 17 to 23, wherein Y_2 is NH.

25. The compound of any one of claims 17 to 24, wherein R_2-R_5 and R_7-$R_{11}$are each independently selected from hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, alkoxy, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

26. The compound of any one of claims 17 to 24, wherein R_2-R_5 and R_7-R_{11} are each independently selected from hydrogen or halo.

27. The compound of any one of claims 1 to 26, wherein B is CH.

28. The compound of any one of claims 1 to 26, wherein B is N.

29. The compound of any one of claims 1 to 28, wherein R_{12a} and R_{12b} are each independently selected from hydrogen, C_1-C_8 alkyl, or C_6-C_{12} aryl, wherein each of said alkyl

or aryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, -NR_2, -N^+R_3, =NR, -CX_3, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO_2, =N_2, -N_3, -NHC(=O)R, -NHS$(=O)_2$R, -C(=O)R, -C(=O)NRR, -S$(=O)_2$OH, -S$(=O)_2$R, -OS$(=O)_2$OR, -S$(=O)_2$NR, -S(=O)R, -OP(=O)$(OR)_2$, -P(=O)$(OR)_2$, -P(=O)$(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_8 alkyl, C_6-C_{12} aryl, C_6-C_{12} aryl C_1-C_8 alkyl, or C_3-C_8 heterocycle.

30. The compound of any one of claims 1 to 29, wherein R12a and R12b are each independently selected from hydrogen, C1-C8 alkyl, or C6-C12 aryl.

31. The compound of any one of claims 1 to 30, wherein R_2 is hydrogen, OH, NO_2, CHO, SO_2, SO_3H, $NR_{12a}R_{12b}$, $SO_2NR_{12a}R_{12b}$, $CONR_{12a}R_{12b}$, halo, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_{12} heteroalkyl, C_3-C_{12} heterocyclyl, or C_6-C_{12} heteroaryl, wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroalkyl, heterocyclyl, or heteroaryl may be optionally substituted by one or more -X, -R, =O, -OR, -SR, -NR_2, -N^+R_3, =NR, -CX_3, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO_2, =N_2, -N_3, -NHC(=O)R, -NHS$(=O)_2$R, -C(=O)R, -C(=O)NRR, -S$(=O)_2$OH, -S$(=O)_2$R, -OS$(=O)_2$OR, -S$(=O)_2$NR, -S(=O)R, -OP(=O)$(OR)_2$, -P(=O)$(OR)_2$, -P(=O)$(OH)_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR.

32. The compound of any one of claims 1 to 31, wherein R_2 is hydrogen or halo.

33. The compound of any one of claims 1 to 32, wherein R_1 is selected from $CONR_{12a}R_{12b}$, COR_{12a}, $COOR_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more -F,- Br, -R, =O, -OR, -SR, -NMeEt, -NEtEt, -N^+R_3, =NR, -CX_3, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO_2, =N_2, -N_3, -NHC(=O)R, -NHS$(=O)_2$R, -C(=O)R, -C(=O)NRR, -S$(=O)_2$OH, -S$(=O)_2$R, -OS$(=O)_2$OR, -S$(=O)_2$NR, -S(=O)R, -OP(=O)$(OR)_2$, -

P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

34. The compound of any one of claims 1 to 33, wherein R_1 is selected from CONR$_{12a}$R$_{12b}$, COR$_{12a}$, COOR$_{12a}$, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 fluoroalkyl, C_1-C_8 bromoalkyl, C_2-C_8 haloalkenyl, C_2-C_8 haloalkynyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkenyl, alkynyl, haloalkenyl, haloalkynyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more -F,- Br, -R, =O, -OR, -SR, -NMeEt, -NEtEt, -N$^+$R$_3$, =NR, -CX$_3$, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO$_2$, =N$_2$, -N$_3$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(OH)$_2$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

35. The compound of any one of claims 1 to 33, wherein R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -F, -Br, -R, =O, -OR, -CX$_3$, -CN, -OCN, -SCN, -N=C=O, -NO$_2$, -NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR, -S(=O)$_2$OH, -S(=O)$_2$R, -OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -C(=O)R, -C(=O)OR, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, halo or perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

36. The compound of any one of claims 1 to 33, wherein R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, or C_1-C_6 alkylene-tetrahydropyranyl, wherein each of said alkyl, alkylene-tetrahydropyranyl, aryl, or cycloalkyl may be optionally substituted by one or more of -F, -Br, -R, =O, -OR, $-CX_3$, -OCN, -SCN, -N=C=O, $-NO_2$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR, $-S(=O)_2OH$, $-S(=O)_2R$, -$OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, -C(=O)R, -C(=O)OR, -C(S)R, -C(O)OR, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, or -C(=NR)NRR;

wherein each X is independently halo; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl, bridged C_6-C_{12} cycloalkyl, perhalo substituted C_3-C_{12} cycloalkyl, or a C_3-C_{12} heterocycle.

37. The compound of any one of claims 1 to 33, wherein R_1 is selected from C_1-C_8 alkyl, C_1-C_8 bromoalkyl, C_1-C_8 fluoroalkyl, C_1-C_8 cyanoalkyl, C_6-C_{12} aryl, C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_3-C_{12} cycloalkyl, C_1-C_6 alkylene- C_6-C_{12} aryl, C_1-C_6 alkylene- C_6-C_{12} fluoroaryl, C_1-C_6 alkylene- C_3-C_{12} heterocycle, C_1-C_6 alkylene-C(=O)NRR;

wherein each of said alkyl, aryl, cycloalkyl, or heterocyclyl may be optionally substituted by one or more bromo or fluoro; and said alkyl may also be optionally substituted by one or more -CN; and

each R is independently H, C_1-C_{10} alkyl, C_6-C_{12} aryl, C_6-C_{12} fluoroaryl, C_6-C_{12} aryl C_1-C_8 alkyl, C_3-C_{12} cycloalkyl.

38. The compound of any one of claims 1 to 33, wherein R_1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, 4-cyano-1-butyl, 3,3-dimethyl-1-butyl, 1- hexyl, 1-heptyl, methylene cyclohexyl, methylene-4,4-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl, methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, methylene-4-tetrahydropyranyl, methyleneC(O)NH(cyclohexyl), methyleneC(O)NH(t-butyl), 1-ethylene-2-(N-morpholinyl), 1-ethylene-2-(N-piperidinyl), and 1-ethylene-2-(4,4-difluoro-N-piperidinyl).

39. The compound of any one of claims 1 to 33, wherein R1 is selected from 1-butyl, 1-pentyl, 5-fluoro-1-pentyl, methylene cyclohexyl, methylene-3,3-difluoro-1-cyclohexyl, methylene-p-fluoro-phenyl, methylene-adamantyl, methylene-N-methyl-2-piperidinyl,

methylene-cycloheptanyl, methylene-2-bicyclo[2.2.1]heptanyl, and methylene-4-tetrahydropyranyl.

40. The compound of any one of claims 1 to 39, wherein R_{6a} and R_{6b} are each independently selected from C_1-C_4 alkyl or R_{6a} and R_{6b} together form a C_3-C_6 cycloalkyl ring or a 3 to 7 membered heterocyclyl ring.

41. The compound of any one of claims 1 to 40, wherein R_{6a} and R_{6b} are each independently selected from C_1-C_4 alkyl or R_{6a} and R_{6b} together form a C_3-C_5 cycloalkyl ring.

42. The compound of any one of claims 1 to 41, wherein R_{6a} and R_{6b} are each methyl or R_{6a} and R_{6b} together form a cyclopropyl or cyclopentyl ring.

43. The compound of any one of claims 1 to 40, wherein R_{6a} and R_{6b} together form a 3 to 6 membered heterocyclyl ring.

44. The compound of claim 43, wherein R_{6a} and R_{6b} together form a 4,4-tetrahydropyranyl ring.

45. The compound of any one of claims 1 to 44, wherein the EC50 of the compound of the invention in a CB_1 and/or CB_2 receptor affinity assay is less than about 50 μM.

46. The compound of any one of claims 1 to 45, wherein the compound has an inhibition of control specific binding of less than about 65% and/or a control specific binding of at least 40% for at least one G-protein coupled receptor or ligand-gated ion channel selected from the group consisting of adenosine A1, adenosine A2A, adenosine A3, adrenergic α1, adrenergic α2, adrenergic β1, adrenergic β2, angiotensin AT1, central benzodiazepine BZD, bradykinin B2, cholecystokinin CCK1, dopamine D1, dopamine D2S, endothelin ETA, GABA (non-selective), galanin GAL2, chemokine CXCR2, chemokine CCR1, histamine H1, histamine H2, melatonin MT1, muscarininc M1, muscarininc M2, muscarininc M3, tachykinin NK2, tachykinin NK3, neuropeptide Y1, neuropeptide Y2, neurotensin NTS1, opioid μ, opioid δ, opioid κ, opioid NOP, prostaglandin EP4, serotonin 5-HT1A, serotonin HT1B, serotonin HT2A, serotonin HT2B, serotonin HT3, serotonin HT5A, serotonin HT6, serotonin HT7, somatostatin SST, vasoactive intestinal polypeptide VPAC1, vasopressin V1A, Ca2+ channel

L, KV channel, SKCa channel, Na+ channel (site 2), Cl- channel (GABA-gated), noradrenaline transporter, dopamine transporter, and serotonin transporter.

47. A pharmaceutical composition comprising a compound of any one of claims 1 to 46, or a pharmaceutically acceptable salt or prodrug thereof and a pharmaceutically acceptable carrier.

48. A compound of any one of claims 1 to 46, or a pharmaceutically acceptable salt or prodrug thereof for use in treating pain in a subject.

49. A compound of any one of claims 1 to 46, or a pharmaceutically acceptable salt or prodrug thereof for use in treating nausea and/or emesis in a subject.

50. A compound of any one of claims 1 to 46, or a pharmaceutically acceptable salt or prodrug thereof for use in stimulating appetite in a subject.

51. A compound of any one of claims 1 to 46, or a pharmaceutically acceptable salt or prodrug thereof for use in inducing a euphoric effect in a subject.

52. A compound of any one of claims 1 to 46, or a pharmaceutically acceptable salt or prodrug thereof for use in relaxing a subject.

53. A compound of any one of claims 1 to 46, or a pharmaceutically acceptable salt or prodrug thereof for use in inducing a positive mood change in a subject.

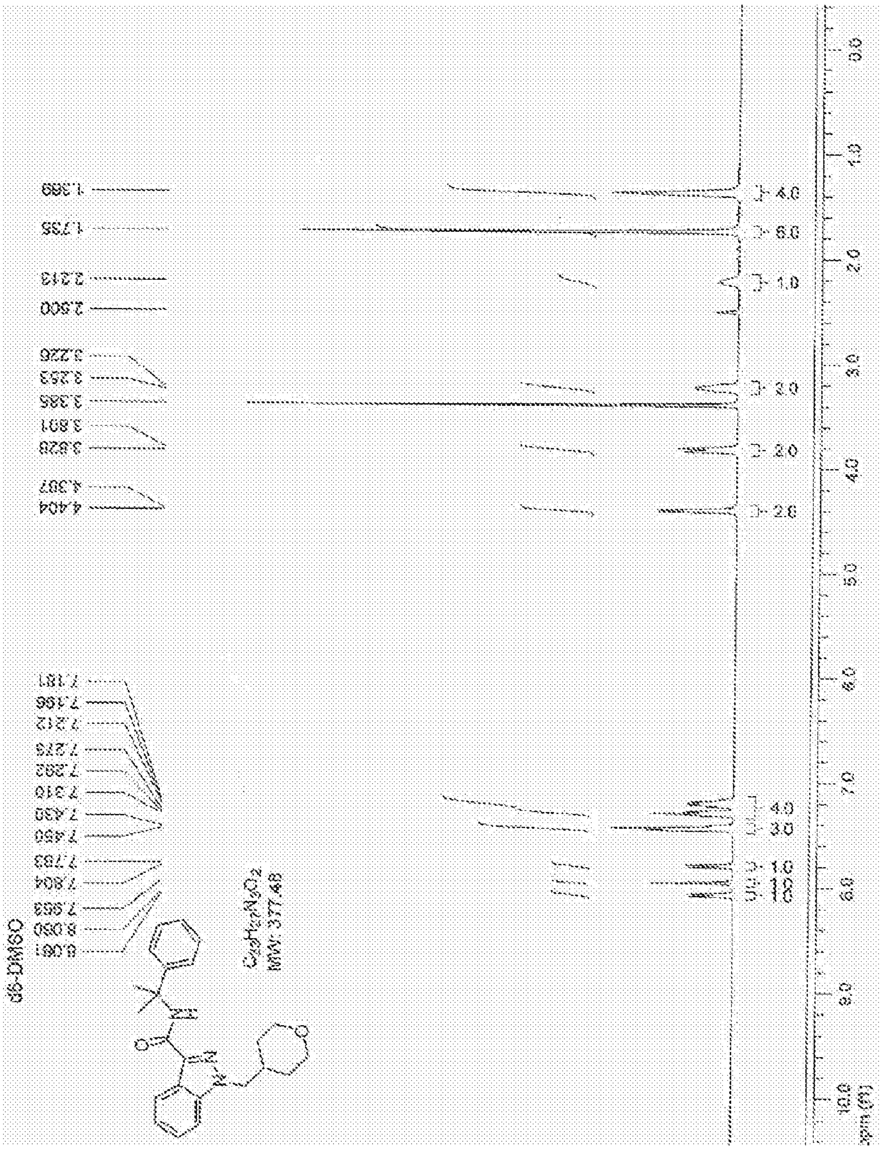

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Fig. 1

2/2

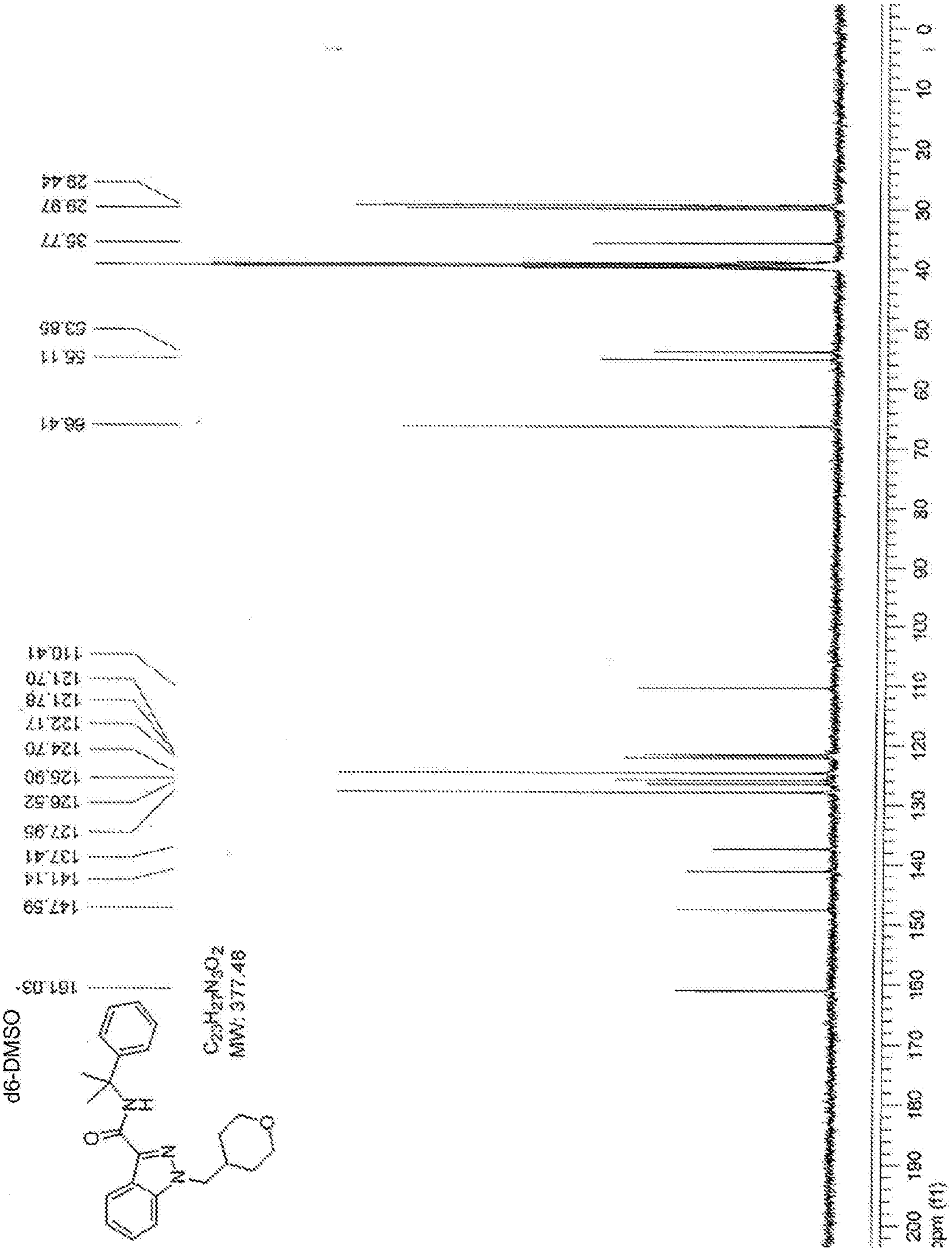

Fig. 2

SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/060636

A. CLASSIFICATION OF SUBJECT MATTER

C07D 209/08 (2006.01) C07D 231/56 (2006.01) A61K 31/416 (2006.01) A61P 43/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, Registry, Sub Structure Search based on formula I and Ia and Applicant Search in Patentscope and European Patent Registry: BOWEN, Mattew James and WILLIAMSON, James Peter Bernard

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

☒ Further documents are listed in the continuation of Box C ☒ See patent family annex

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

Date of the actual completion of the international search 1 July 2014	Date of mailing of the international search report 01 July 2014
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	**Authorised officer** Ricky Fung AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262223648

INTERNATIONAL SEARCH REPORT	International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT	**PCT/IB2014/060636**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemical Abstract Acession Number: 2009:666523 STN Entry Date: 2009 & Biechy, A and Zard, S. Z "A Flexible, Convergent Approach to Polycyclic Indole Structures: Formal Synthesis of (±)-Mersicarpine" Organic Letters (2009), 11(13), pp 2800-2803 See Abstract and RN 1165634-82-2	1, 2, 5-8, 10-13, 27, 31-34, 40-42
A	Chemical Abstracts Accession Number: 1999:375527; STN Entry Date: 1999. & WO 1999/028297 See abstract, CAS RNs 226898-58-4 and 226900-97-6	1-53

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/IB2014/060636**

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.