NOVEL ARYLATED CAMPHENES, PROCESSES FOR THEIR PREPARATION AND USES THEREOF

FIELD OF THE INVENTION

This invention relates to arylated camphenes, processes for their preparation and uses thereof for the manufacture of medicaments for the treatment of diseases, disorders or conditions associated with, or benefiting from stimulation of CB2 receptors.

BACKGROUND OF THE INVENTION

The following publications are relevant for describing the state of the art in the field of the invention:

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Two cannabinoid receptors have been well characterized so far - the CB1 receptor, which is present mainly in the central nervous system (CNS), (and to a lesser extent in the periphery), and the CB2 receptor which is considered mainly a peripheral receptor. Natural stimulation of the CB1 receptor, which is produced by the endogenous cannabinoids, when and where needed, is central to many of our physiological systems.

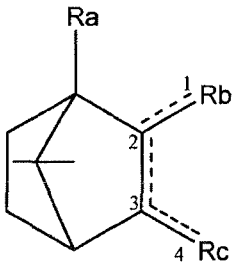
However exogenous administration of CB1 agonists (such as the marijuana constituent THC) may lead to undesirable side effects. Therefore CB1 agonists, which act on the central nervous system, are of limited therapeutic value (for a recent review see Kogan and Mechoulam, 2007).

The CB2 receptor is present in low levels in the CNS, mainly in glial cells. However, numerous neurological conditions have been shown to induce expression of this receptor in the brain. Some of these conditions are cerebral hypoxia-ischemia, cerebral artery occlusion, Alzheimer's disease and Huntington's disease. It was further shown that stimulation of the CB2 receptor is not accompanied by undesirable CNS or other effects, such as major and/or detrimental psychoactive effects, usually associated with the stimulation of the CB1 receptor (Ashton and Glass, 2007).

There is therefore a need for selective CB2 receptor stimulants, capable of being utilized for treating diseases, disorders or conditions associated with, or benefiting from such stimulation of CB2 receptors.

SUMMARY OF THE INVENTION

The present invention provides a compound of general formula (I):



(I)

wherein

1 ------ 2, 2 ------ 3, 3 ------ 4 are each independently a single or double bond;

R_a is selected from straight or branched C_1-C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl and -C(=O)R_d, each optionally substituted by at least one group selected from –OH, -COOH, -NH_2, C_1-C_5 amine, halogen, phenyl, heteroaryl; wherein

R_d is selected from the group consisting of -H, –OH, straight or branched C_1-C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl, straight or branched C_1-C_5 alkoxy, -NR_eR_f;

R_e and R_f are each independently selected from H and straight or branched C_1-C_5 alkyl; and

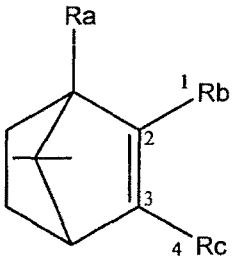
R_b and R_c are each independently selected from -H, -OH, =O, $=CR_gR_h$, $=NR_i$, =S, -C_5-C_{15}, aryl ring substituted by at least one group selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, C_1-C_{12} alkoxycarboxylic acid, -OH, $-OC(=O)R_p$ and $-C(=O)R_q$; wherein

R_g, R_h, R_i, R_p and R_q are each independently selected from H, straight or branched C_1-C_5 alkyl, straight or branched C_1-C_5 alkoxy and NH_2; and

provided that at least one of R_b and R_c is said substituted -C_5-C_{15} aryl ring.

In some embodiments of the invention at least one of ^{1}------^{2}, ^{2}------^{3}, ^{3}------^{4} is a double bond.

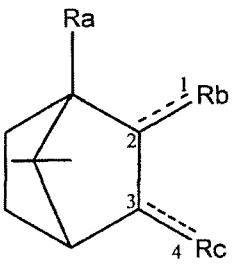
In one embodiment of the present invention, ^{2}------^{3} of compound of formula (I) is a double bond. Consequently, compound of formula (I) is a compound of formula (I'):



(I')

wherein substituents R_a, R_b and R_c are as defined herein above.

In another embodiment of the present invention, ^{2}------^{3} of a compound of formula (I) is a single bond. Consequently, compound of formula (I) is a compound of formula (I''):



(I'')

wherein substituents R_a, R_b and R_c are as defined herein above.

In one embodiment, 1=2 is a double bond. According to this embodiment, 2=3 is a single bond and 3=4 may be either a single or double bond.

In another embodiment, 3=4 is a double bond. According to this embodiment, 2=3 is a single bond and 1=2 may be either a single or double bond.

In a further embodiment 1=2 is a single bond and 3=4 is a single bond.

In another embodiment of the invention, at least one of R_b and R_c is a phenyl ring substituted by at least two substituent selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} alkoxycarboxylic acid, -C(=O)OH, -C(=O)NH_2, -C(=O)(C_1-C_5alkyl), -C(=O)(C_1-C_5alkoxy), -OC(=O)H, -OC(=O)NH_2, -OC(=O)(C_1-C_5alkyl). Thus, in one embodiment R_b is a phenyl ring substituted by at least two substituent selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, C_1-C_{12} alkoxycarboxylic acid, -COOH, -$CONH_2$, -C(=O)(C_1-C_5alkyl), -C(=O)(C_1-C_5alkoxy), -OCOH, -OC(=O)NH_2, -OC(=O)(C_1-C_5alkyl) and R_c is selected from -H, -OH, =O, $=CR_gR_h$, $=NR_i$, =S, -C_5-C_{15} aryl ring substituted by at least one group selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, C_1-C_{12} alkoxycarboxylic acid, –OC(=O)R_p and –C(=O)R_q; wherein R_g, R_h, R_i R_p and R_q are each independently selected from H, straight or branched C_1-C_5 alkyl, straight or branched C_1-C_5 alkoxy and NH_2. In another embodiment, R_c is a phenyl ring substituted by at least two substituent selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy -COOH, -$CONH_2$, -C(=O)(C_1-C_5alkyl), -C(=O)(C_1-C_5alkoxy), -OCOH, -OC(=O)NH_2, -OC(=O)(C_1-C_5alkyl) and R_b is selected from -H, -OH, =O, $=CR_gR_h$, $=NR_i$, =S, -C_5-C_{15} aryl ring substituted by at least one group selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, C_1-C_{12} alkoxycarboxylic acid, –OC(=O)R_p and –C(=O)R_q; wherein R_g, R_h, R_i R_p and R_q are each independently selected from H, straight or branched C_1-C_5 alkyl, straight or branched C_1-C_5 alkoxy and –NH_2.

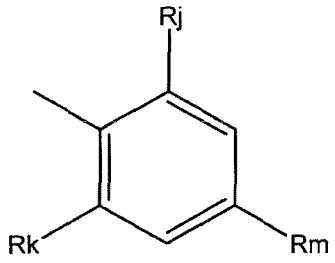
In another embodiment of the invention, at least one of R_b and R_c is a phenyl ring substituted by at least three substituent selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, -C(=O)OH, -C(=O)NH_2,

-C(=O)(C_1-C_5alkyl), -C(=O)(C_1-C_5alkoxy), -OC(=O)H, -OC(=O)NH_2, -OC(=O)(C_1-C_5alkyl).

In some embodiments of the invention when all of 1------2, 2------3, 3------4 represent a single bond, at least one of R_b and R_c is a -C_5-C_{15} aryl ring being substituted by at least two substituents selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, C_1-C_{12} alkoxycarboxylic acid, -OC(=O)R_p and -C(=O)R_q; wherein R_g, R_h, R_i, R_p and R_q are each independently selected from H, straight or branched C_1-C_5 alkyl, straight or branched C_1-C_5 alkoxy and NH_2.

In other embodiments, of the invention when all of 1------2, 2------3, 3------4 represent a single bond, at least one of R_b and R_c is a -C_5-C_{15} aryl ring being substituted by at least three substituents selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, C_1-C_{12} alkoxycarboxylic acid, -OC(=O)R_p and -C(=O)R_q; wherein R_g, R_h, R_i, R_p and R_q are each independently selected from H, straight or branched C_1-C_5 alkyl, straight or branched C_1-C_5 alkoxy and NH_2

In another embodiment of the present invention, at least one of R_b and R_c is a group of formula (II):

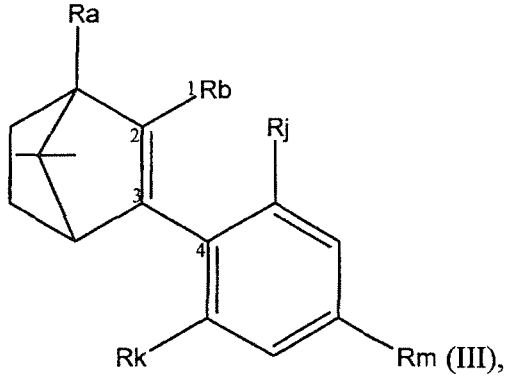


(II)

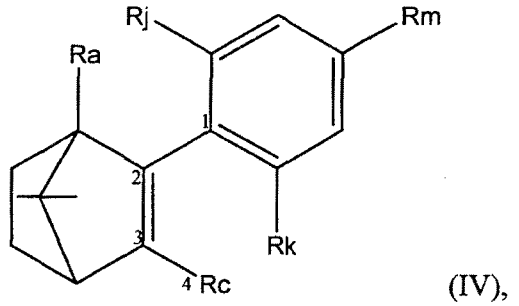
wherein R_j and R_k are each independently selected from H, and –OR_n wherein R_n is selected form H, -$COOR_t$, a straight or branched C_1-C_5 alkyl optionally substituted by at least one group selected from –COOH, -NH_2, provided that at least one of R_j and R_k is different than H; and R_m is selected from a straight or branched C_6-C_{12} alkyl, a straight or branched C_5-C_9 alkoxy, a straight or branched C_1-C_7 ether; each optionally substituted by at least one group selected from –COOH, -NH_2 ; and R_t is selected from H, C_1-C_5 alkyl and -NH_2.

Thus, a compound of the invention may be a compound of any one formulae

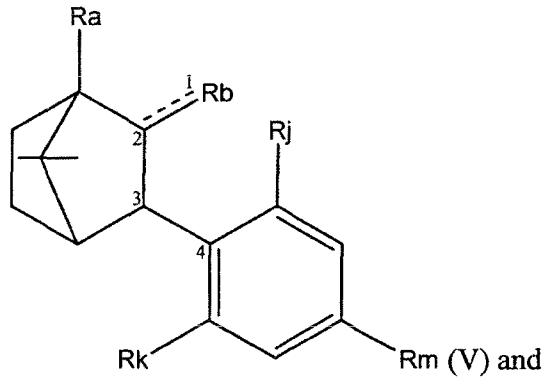
(III), (IV), (V) or (VI):



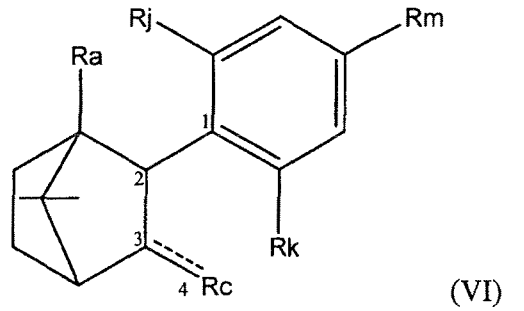
(III),



(IV),



(V) and

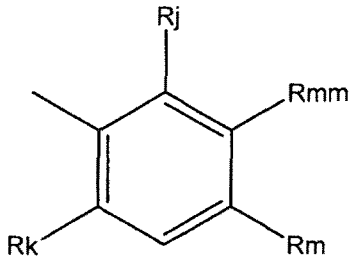


(VI)

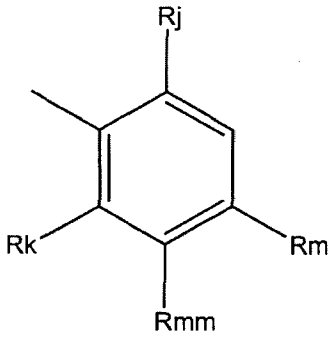
wherein R_j and R_k are each independently H or $-OR_n$ wherein R_n is selected from H, $-COOR_t$, a straight or branched C_1-C_5 alkyl optionally substituted by at least one group selected from –COOH, $-NH_2$, provided that at least one of R_j and R_k is different than H; and R_m is a straight or branched C_6-C_{12} alkyl and R_t is selected from H, C_1-C_5 alkyl and $-NH_2$.

In another embodiment of the present invention, R_a is selected from an straight or branched C_1-C_5 alkyl and -C(=O)R_d, each optionally substituted by at least one group selected from –OH, -COOH, -NH_2, C_1-C_5 amine, halogen, phenyl, heteroaryl and R_d is as defined herein above.

In another embodiment of the present invention, at least one of R_b and R_c is a group of formula (II') or (II''):



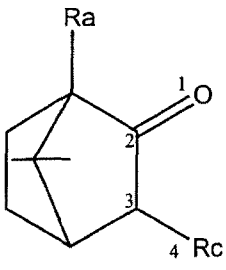
(II')



(II'')

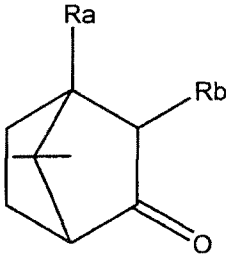
wherein R_j , R_k and R_{mm} are each independently selected from H, and –OR_n wherein R_n is selected form H. -$COOR_t$, a straight or branched C_1-C_5 alkyl optionally substituted by at least one group selected from –COOH, -NH_2, provided that at least one of R_j and R_k is different than H; and R_m is selected from an optionally substituted straight or branched C_3-C_{12} alkyl, an optionally substituted straight or branched C_5-C_9 alkoxy, an optionally substituted straight or branched C_1-C_7 ether; and R_t is selected from H, C_1-C_5 alkyl and -NH_2.

In a further embodiment of a compound of formula (I), when ^{2}------^{3} is a single bond, R_b and R_c are each independently selected from -H, -OH, =O, =CR_gR_h, =NR_i, =S, -C_5-C_{15} aryl ring substituted by at least two substituent selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, -OC(=O)R_p and –C(=O)R_q; wherein R_g, R_h, R_i, R_p and R_q are each independently selected from H, straight or branched C_1-C_5 alkyl, straight or branched C_1-C_5 alkoxy and –NH_2; and provided that at least one of R_b and R_c is said substituted -C_5-C_{15} aryl ring. In a further embodiment, said R_b is =O, thus a compound of the invention may be a compound of formula (VII), wherein R_c is said substituted -C_5-C_{15} aryl ring:



(VII).

In yet a further embodiment, R_c is =O, thus a compound of the invention may be a compound of formula (VIII), wherein R_b is said substituted -C_5-C_{15} aryl ring:



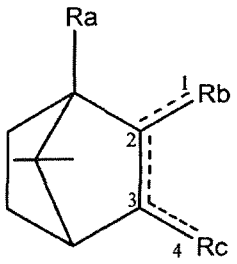
(VIII).

In one embodiment, a compound of the invention is selected from the following list:

- methyl-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate;
- methyl-2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate;
- 2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene;
- (2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol;
- (2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol;
- 2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid;
- 2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid;
- 3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene;

- 3-(2,6-dimethoxy-4-pentylphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one;
- 3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one;
- 3-(2,6-dimethoxy-4-pentylphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol;
- 3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol
- (3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol;
- 3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid;
- methyl 3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate;
- (3-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol;
- 3-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid;
- 5-(2-methyloctan-2-yl)-2-(4,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)benzene-1,3-diol;
- 2-(4-(hydroxymethyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-2-yl)-5-(2-methyloctan-2-yl)benzene-1,3-diol;
- 3-(2,6-dihydroxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid;
- 2-(4-(hydroxymethyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-yl)-5-(2-methyloctan-2-yl)benzene-1,3-diol;
- 5-(2-methyloctan-2-yl)-2-(4,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)benzene-1,3-diol; and
- 3-(2,6-dihydroxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]heptane-1-carboxylic acid.

The invention further provides a compound of general formula (I):



(I)

wherein

1 ═══ 2, 2 ═══ 3, 3 ═══ 4 are each independently a single or double bond;

R_a is selected from an straight or branched C_1-C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl and -C(=O)R_d, each optionally substituted by at least one group selected from –OH, -COOH, -NH_2, C_1-C_5 amine, halogen, phenyl, heteroaryl; wherein

R_d is selected from the group consisting of -H, –OH, straight or branched C_1-C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl, straight or branched C_1-C_5 alkoxy, -NR_eR_f;

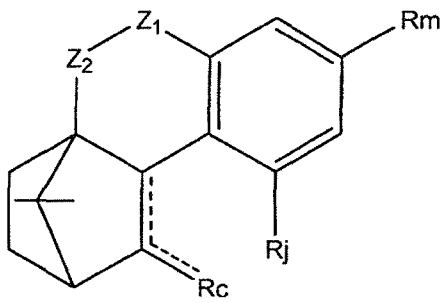
R_e and R_f are each independently selected from H and straight or branched C_1-C_5 alkyl; and

R_b and R_c are each independently selected from -H, -OH, =O, =CR_gR_h, =NR_i, =S, -C_5-C_{15} aryl ring substituted by at least one group selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, C_1-C_{12} alkoxycarboxylic acid, -OH, –OC(=O)R_p and –C(=O)R_q; wherein R_g, R_h, R_i, R_p and R_q are each independently selected from H, straight or branched C_1-C_5 alkyl, straight or branched C_1-C_5 alkoxy and –NH_2;

or R_a and R_b may form a ring together with the carbon atoms they are each attached to; said ring may be a cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, cycloalkenyl, cycloalkynyl, cycloheteroalkynyl ring; in some embodiments said ring is a 6 to 12 member ring;

provided that at least one of R_b and R_c is said substituted -C_5-C_{15} aryl ring.

In some embodiments, a compound of the invention has the general formula (XII):



(XII)

wherein ------ is a single or double bond;

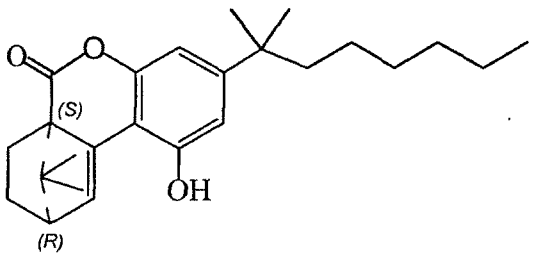
R_c is selected from -H, -OH, =O, $=CR_gR_h$, $=NR_i$, =S, $-C_5$-C_{15} aryl ring substituted by at least one group selected from a straight or branched C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, amine, C_1-C_{12} alkoxycarboxylic acid, $-OC(=O)R_p$ and $-C(=O)R_q$; wherein R_g, R_h, R_i, R_p and R_q are each independently selected from H, straight or branched C_1-C_5 alkyl, straight or branched C_1-C_5 alkoxy and $-NH_2$;

R_j is selected from H, and $-OR_n$ wherein R_n is selected form H, $-COOR_t$, a straight or branched C_1-C_5 alkyl optionally substituted by at least one group selected from –COOH, $-NH_2$; and R_t is selected from H, C_1-C_5 alkyl and $-NH_2$;

R_m is selected from a straight or branched C_6-C_{12} alkyl, a straight or branched C_5-C_9 alkoxy, a straight or branched C_1-C_7 ether; each optionally substituted by at least one group selected from –COOH, $-NH_2$;

Z_1 and Z_2 are each independently selected from –O-, straight or branched C_1-C_5-alkylene, -S-, -C(=O)- and -C(=S)-.

In other embodiments, a compound of the invention may be selected from the group consisting of:



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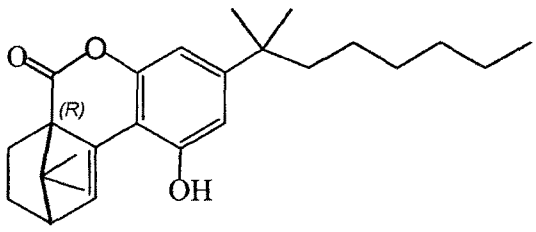

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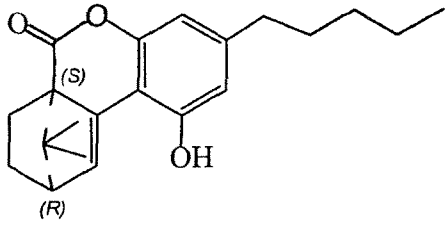

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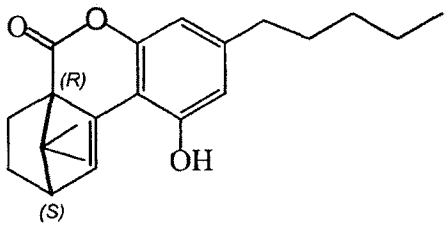


(29).

As used herein, the term "*alkyl*" refers to a straight or branched chain hydrocarbon having from one to five carbon atoms, or from one to seven carbon atoms, or from five to nine carbon atoms, or from six to twelve carbon atoms. Examples of "*alkyl*" as used herein include, but are not limited to, methyl, ethyl, propyl, n-butyl, n-pentyl, isobutyl, and isopropyl, tert-butyl, and the like.

As used herein, the term *"alkenyl"* represents a branched or straight hydrocarbon group having from 2 to 5 or from 2 to 12 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, isopropenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 1-hexenyl, 2-hexenyl and the like.

As used herein, the term "*alkynyl*" represents a branched or straight hydrocarbon group having from 2 to 5 or from 2 to 12 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 1-hexynyl, 2-hexynyl and the like.

As used herein the term "*aryl*" refers to aromatic monocyclic or multicyclic groups containing from 5 to 15 carbon atoms. Aryl groups include, but are not limited to

groups such as unsubstituted or substituted fluorenyl, unsubstituted or substituted phenyl, and unsubstituted or substituted naphthyl. When referring to said aryl being substituted, said substitution may be at any position on the ring, other than the point of attachment to the other ring system of a compound of the invention. Therefore, any hydrogen atom on the aryl ring may be substituted with a substituent defined by the invention. In embodiments where the aryl is a phenyl ring, said substitution may be at the *meta-* and/or *ortho-* and/or *para-* position relative to the point of attachment.

As used herein the term "*heteroaryl*" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, quinolinyl and isoquinolinyl,

As used herein, the term "*C_1-C_{12} alkoxycarboxylic acid*" refers to a –O-(C_1-C_{12} alkylene)-COOH radical.

As used herein the term "*alkylene*" refers to a saturated, divalent, branched or straight hydrocarbon group having from one to five carbon atoms. Non-limiting examples of C_{1-5}-alkylene groups include, methylene, ethylene, 1,2-propylene, 1,3-propylene, butylene, isobutylidene, pentylene, hexylene and the like.

As used herein the term "*ester*" is meant to encompass an –COOR group wherein R is an alkyl as defined herein above.

A used herein the term "*ether*" refers to an –R'OR group, wherein R' is a C_1-C_7 straight or branched alkylene group and R is a C_1-C_7 straight or branched alkyl group.

As used herein, the term "*alkoxy*" refers to an RO- group, where R is alkyl as defined above.

As used herein the term "*C_1-C_7 amide*" refers to a monoalkyl amide (-CONHR) or dialkyl amide (-CONRR'), wherein R and R' are independently a C_1-C_7 straight or branched alkyl.

As used herein the term "*C_1-C_5 amine*" refers to an –NHR or –NRR' group wherein R and R' are independently a C_1-C_5 straight or branched alkyl.

The term "*optionally substituted*" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents such as for example those specified above and phenyl, substituted phenyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, halogen (-F, -Cl, -Br, -I), -COOH, $-NH_2$, -NHR and -NRR' wherein R and R' are each independently a straight or branched C_1-C_5 alkyl. When the groups are substituted with more than one substituent the substituents may be the same or different and said substitution may occur at any position on the substituted group (i.e. at a terminal or any mid-chain position or both).

The term "*cycloalkyl*" refers to a cyclic ring having from 6 to 12 carbon atoms connected via single bond only.

The term "*cycloalkenyl*" refers to a cyclic ring having from 6 to 12 carbon atoms connected having at least one double bond.

The term "*cycloalkynyl*" refers to a cyclic ring having from 6 to 12 carbon atoms connected having at least one triple bond.

The term "*cycloheteroalkyl*" refers to a cyclic ring having from 6 to 12 carbon atoms connected via single bond only, wherein at least one carbon atom is replaced with a heteroatom selected from N, O, S.

The term "*cycloheteroalkenyl*" refers to a cyclic ring having from 6 to 12 carbon atoms connected having at least one double bond, wherein at least one carbon atom is replaced with a heteroatom selected from N, O, S.

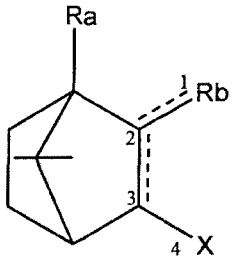
The term "*cycloheteroalkynyl*" refers to a cyclic ring having from 6 to 12 carbon atoms connected having at least one triple bond, wherein at least one carbon atom is replaced with a heteroatom selected from N, O, S.

It is appreciated by a person skilled in the art that certain compounds of the invention may posses at least one stereogenic carbon atom. Thus, it should be noted that the present invention encompasses all possible stereosiormers of such compounds including all possible mixtures thereof (such as for example racemic mixtures, diastereomeric mixtures, non-racemic mixtures etc.). It is further noted that compounds of the invention may posses a double bond. Thus, the present invention encompasses any stereoisomer (*cis*, *trans*, *E* or *Z* stereoisomers) of such compounds including any mixture thereof.

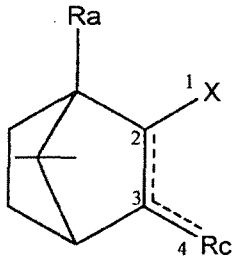
The invention further provides processes for the preparation of compounds of the invention.

In one aspect the invention provides a process for the preparation of a compound of general formula (I), as defined herein above, said process comprising:

(a) providing a compound having the general formula (X) or (X'):



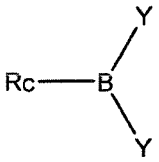
(X)



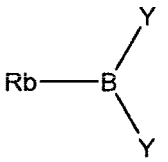
(X')

wherein R_a, R_b and R_c have the same meaning as defined herein above; X is a halide, pseudohalide, functional leaving group (such as for example –OTf and similar functional groups capable of being easily removed upon coupling reaction); and 1=====2, 2=====3, 3=====4 are each independently a single or double bond;

(b) reacting compound (X) or (X') with a compound having the general formula (XI) or (XI') respectively:



(XI')



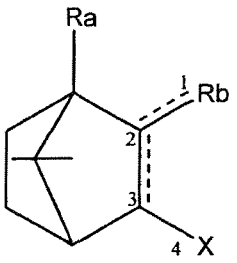
(XI)

wherein each of Y is selected from OH, C_1-C_5 alkoxy or both may form a cyclic dialkoxy ring together with the boron atom they are attached to,

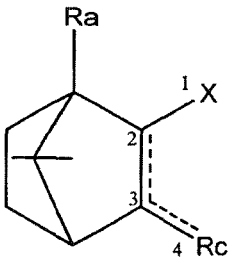
in the presence of a catalyst; thereby obtaining a compound of formula (I).

In another aspect the invention provides a process for the preparation of a compound of general formula (I), as defined herein above, said process comprising:

(a) providing a compound having the general formula (X) or (X'):



(X)



(X')

wherein R_a, R_b and R_c have the same meaning as defined herein above; X is a halide, pseudohalide, functional leaving group (such as for example –OTf and similar functional groups capable of being easily removed upon coupling reaction); and 1=2, 2=3, 3=4 are each independently a single or double bond;

(b) coupling compound (X) or (X') with R_c-H or R_b-H respectively; thereby obtaining a compound of formula (I). In some embodiments said coupling process is a *halogen-metal exchange* process, as detailed herein below.

Such processes include for example *Suzuki cross-coupling* reactions as follows:

1. Methylation of (±) ketopinic acid with methyl iodide and potassium carbonate in dimethylformamide thereby obtaining (±) methyl ketopinate;

2. Enolization of (±) camphor/(±) epicamphor/(±) methyl ketopinate by lithium diisopropylamide and the addition of phenyl triflimide in tetrahydrofuran to afford corresponding (±) vinyl triflate;

3. Lithiation of 2,6-dimethyl ether-4-alkyl resorcinol by n-butyl lithium and formation of aryl boronic ester using isopropyl pinacol borate in tetrahydrofuran;

4. Cross-coupling reaction between aryl boronic ester and (±) vinyl triflate catalyzed by tetrakis-palladium triphenyl phosphine in the presence of tert-butyl ammonium fluoride in tetrahydrofuran to obtain corresponding (±) arylated bornene;

5. Reduction of (±) arylated methyl ketopinate by lithium aluminium hydride in tetrahydrofuran to afford corresponding alcohol;

6. Hydrolisis of (±) arylated methyl ketopinate by lithium hydroxide in methanol/water to obtain corresponding acid.

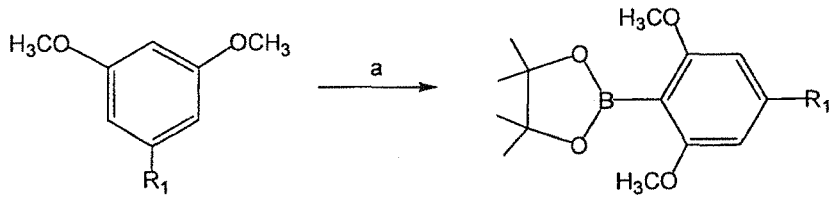
Another alternative process for the manufacture of compounds of the invention include *halogen-metal exchange* process as follows:

1. Lithiation by n-butyl lithium and copper iodide metalation of 2,6-dimethyl ether-4-alkyl resorcinol promoted coupling reaction with (+) 3-bromocamphor in diethyl ether and dimethyl sulfoxide to obtain corresponding arylated camphor

2. Reduction of camphoric carbonyl by lithium aluminium hydride in tetrahydrofuran to afford corresponding alcohol.

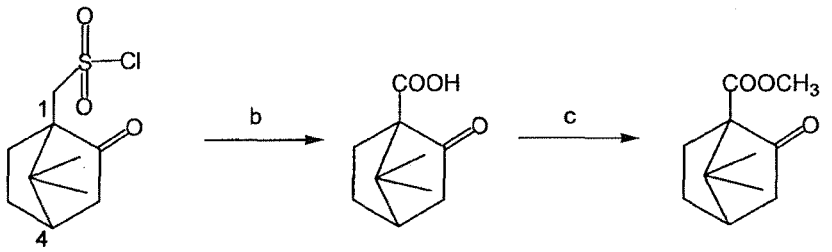
Exemplary synthetic procedures for the manufacture of compounds of the invention are described in Schemes 1 and 2.

Scheme1[a]. Cross-coupling reaction at the **C2**-position of camphoric moiety.



1 - R_1: l',l'-dimethylheptyl
2 - R_1: n-pentyl

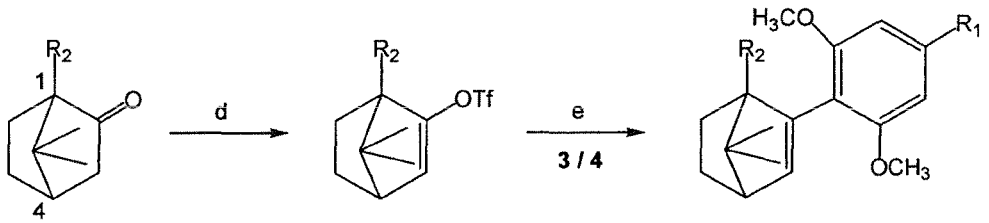
3- R_1: l',l'-dimethylheptyl(DMH)
4- R_1: n-pentyl(C_5H_{11})



5a-(1R,4S)
5b-(1S,4R)

6a-(1R,4S)
6b-(1S,4R)

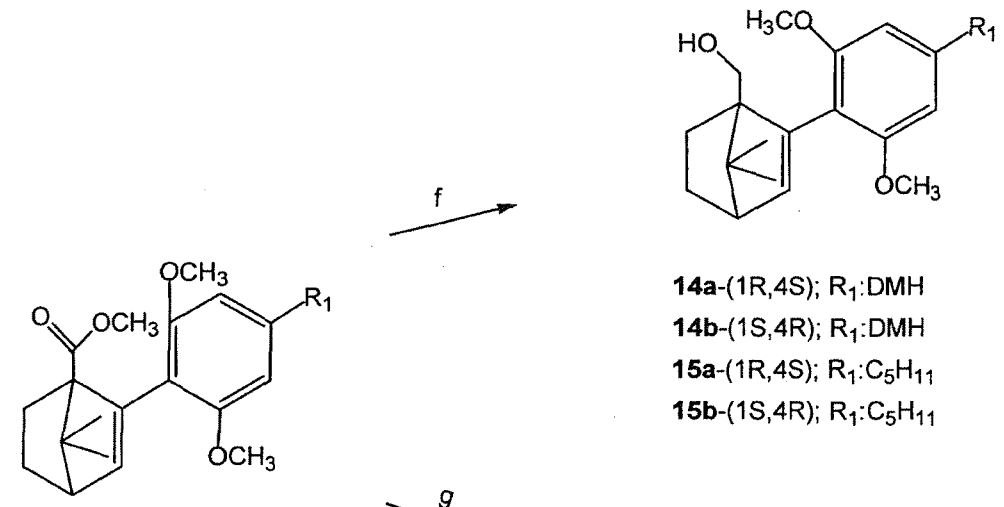
7a-(1R,4S)
7b-(1S,4R)



7a-(1R,4S); R2:$COOCH_3$
7b-(1S,4R); R2:$COOCH_3$
8a-(1R,4R); R_2:CH_3
8b-(1S,4S); R_2:CH_3

9a-(1R,4S); R2:$COOCH_3$
9b-(1S,4R); R2:$COOCH_3$
10a-(1R,4R); R_2:CH_3
10b-(1S,4S); R_2:CH_3

11a-(1R,4S); R_1:DMH; R_2:$COOCH_3$
11b-(1S,4R); R_1:DMH; R_2:$COOCH_3$
12a-(1R,4R); R_1:DMH; R_2:CH_3
12b-(1S,4S); R_1:DMH; R_2:CH_3
13a-(1R,4S); R_1:C_5H_{11}; R_2:$COOCH_3$
13b-(1S,4R); R_1:C_5H_{11}; R_2:$COOCH_3$



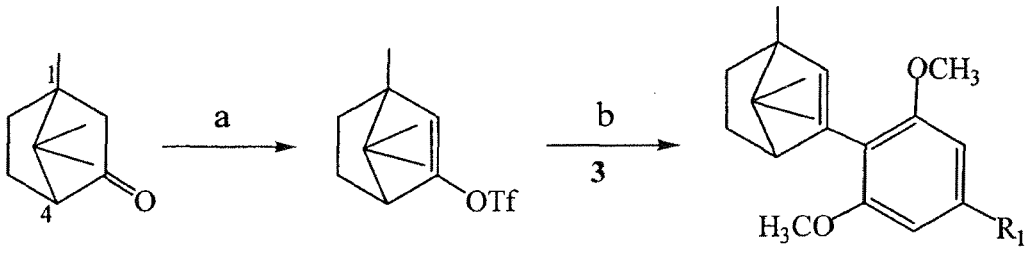
14a-(1R,4S); R_1:DMH
14b-(1S,4R); R_1:DMH
15a-(1R,4S); R_1:C_5H_{11}
15b-(1S,4R); R_1:C_5H_{11}

11a-(1R,4S); R_1:DMH
11b-(1S,4R); R_1:DMH
13a-(1R,4S); R_1:C_5H_{11}
13b-(1S,4R); R_1:C_5H_{11}

16a-(1R,4S); R_1:DMH
16b-(1S,4R); R_1:DMH
17a-(1R,4S); R_1:C_5H_{11}
17b-(1S,4R); R_1:C_5H_{11}

[a]Reagents and conditions: (a) n-BuLi, THF, 0°C, PINBOP, -78°C. (b) Na_2CO_3, H_2O, $KMnO_4$, reflux. (c) K_2CO_3, DMF, MeI, r.t. (d) LDA, THF, -78°C, phenyl triflimide, 0°C to r.t. (e) $Pd(PPh_3)_4$, t-BuNF, THF, reflux. (f) $LiAlH_4$, THF, 0° to r.t. (g) LiOH, MeOH/H_2O 3:1, 200°C.

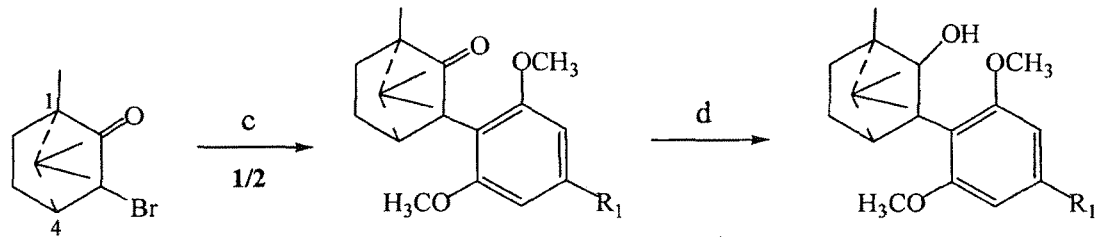
Scheme 2[a]. Cross-coupling reactions substituted at **C3**-position of camphoric moiety.



18a-(1S,4S)
18b-(1R,4R)

19a-(1S,4S)
19b-(1R,4R)

20a-(1S,4S); R1:DMH
20b-(1R,4R); R1:DMH



21-(1R,4S) **22** - R_1:C_5H_{11} **23** - R_1:DMH **24** - R_1:C_5H_{11} **25** - R_1:DMH

[a]Reagents and conditions: (a) LDA, THF, -78°C, phenyl triflimide, 0°C to r.t. (b) $Pd(PPh_3)_4$, t-BuNF, THF, reflux. (c) n-BuLi, diethyl ether, 0°C to r.t., CuI, diethyl ether/DMSO. (d) $LiAlH_4$, diethyl ether, 0°C to reflux.

In a further embodiment a compound of the invention is capable of stimulating a CB receptor.

The term "*CB receptor*" is meant to encompass a cannabinoid G-protein coupled receptor, defined by their capability to bind to cannabinoids and/or endocannabinoids. In one embodiment said receptor is a CB2 receptor (cannabinoid receptor Type 2). In another embodiment said stimulation of a CB2 receptor is associated with the treatment of a disease, disorder or condition.

When referring to "*stimulation*" of a composition of the invention to a CB receptor it is meant to include any degree of excitation of a CB receptor to allow activation of said receptor, such as for example agonistic effect of a compound of the invention on said CB receptor. It is noted that in order for such a stimulation to be achieved an association between a compound of the invention and said receptor should be established. A compound of the present invention may be associated with said receptor via any type of interaction such as for example covalent bonding, electrostatic bonding (such as for example hydrogen bonding, π or σ interactions, London dispersion forces, Van-Der-Waals forces etc.), ionic bonding, metallic bonding etc.

CB2 receptor stimulation has been shown to be of considerable medical value (Ashton and Glass, 2007). Some effects relevant to our patent are listed below:

1. Selective CB2 receptor stimulation causes potent anti-inflammatory effects in a diverse range of animal models (Ashton and Glass, 2007; Benito et al. 2008); lowers neuropathic pain (Yamamoto et al., 2008); inhibits secretion of pro-inflammatory cytokines (Klegeris et al., 2003).

2. CB2 receptor agonists stimulate osteoblast function and inhibit osteoclasts leading to increased bone formation. These effects are of major relevance to osteoporosis (Ofek et al., 2005).

3. CB2 receptor stimulation retards progression of atherosclerosis in an animal model (Stefens et al., 2005; Steffens and Mach, 2006). As cerebral hypoxia-ischemia and middle cerebral artery occlusion induce expression of the CB2 receptor, such agonists may lower the effects of these conditions (Ashton et al., 2006).

4. Selective CB2 receptor stimulation has been shown to lower hepatic encephalopathy (a neuropsychiatric complication occurring in both acute and chronic liver failure) and to display anti-fibrinogenic effects (Avraham et al., 2006; Dagon et al., 2007; Lotersztajn et al., 2008).

5. CB2 receptor stimulation has the potential to block progression of Alzheimer's disease (Benito et al., 2008), Huntington's disease (Fernandez-Ruiz et al. 2005), amyotrophic lateral sclerosis (Bilsland et al., 2006; Centonze et al., 2007), multiple sclerosis (Docagne et al., 2008) and myelin disorders (Arevalo-Martin et al., 2008). For a general review see Fernandez-Ruiz et al., (2008).

6. Cannabinoid CB2 receptor activation decreases cerebral infarction in a mouse focal ischemia/reperfusion model and a CB1 antagonist together with a CB2 agonist improved cerebral blood flow (Zhang et al. 2008).

7. CB2 receptor stimulation helps the establishment of ischemic preconditioning (a potent endogenous form of tissue protection against ischemia-reperfusion in various organs) (Pacher and Hasko, 2008).

8. CB2 receptor stimulation causes inhibition of emesis (van Sickle et al., 2005).

9. CB2 cannabinoid agonists stimulate neural progenitor proliferation (Palazuelos et al., 2006, 2008). This effect may be associated with improvement of neural damage.

In the context of the present invention the term "*treatment*" is meant to encompass the management and care of a patient for the purpose of combating a disease, disorder or condition. The term is intended to include the delaying of the progression of a disease, disorder or condition, the alleviation or relief of symptoms and complications, and/or the cure or elimination of the disease, disorder or condition. The patient to be treated is preferably a mammal, in particular a human being. This term

refers to the administration of a therapeutic amount of a compound of the invention which is effective in one of the following: ameliorating undesired symptoms associated with a disease, disorder, or pathological condition; effective in preventing the manifestation of such symptoms before they occur; effective in slowing down the progression of a disease or disorder; effective in slowing down the deterioration of a disease, disorder or condition; effective in prolonging the time period onset of remission period; effective in slowing down the irreversible damage caused in a progressive chronic stage of a disorder; effective to delay the onset of said progressive; effective to lessen the severity or cure the disease or disorder; effective to improve survival rates of individuals infected with the disease, or effective to prevent the disease form occurring altogether (for example in an individual generally prone to the disease) or a combination of two or more of the above.

Thus, in one embodiment of the present invention, said disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof.

In a further embodiment, said disease, disorder or condition is cerebral injury. In another embodiment said cerebral injury is brain trauma selected from closed head injury, penetrating head injury, blast injury, cerebral ischemic-reperfusion injury, post-operable brain injury, brain hemorrhaging.

In another embodiment said compound of the invention is capable of lowering the secondary damage produced by brain trauma.

The term "*cerebral injury*", "*brain trauma*" or "*traumatic brain injury*" as used herein interchangeably is meant to encompass any traumatical injury to the brain, which may be caused by an external impac force (such as rapid acceleration or deceleration, impact, blast waves, or penetration by a projectile) or by any disease or disorder (such as for example ischemia, stroke, infection or anyurism).

Brain trauma can be classified based on severity, mechanism (closed or penetrating head injury), or other features (e.g. occurring in a specific anatomical location or over a widespread area in the brain). Head injuries can also be classified into

mild, moderate, and severe categories and may be diagnosed using different International scales measuring for example the level of consciousness of the injured subject.

In addition to the damage caused at the moment of injury, brain trauma causes secondary injury (secondary damage produced by brain trauma), which is manifested in a variety of events that take place within minutes and/or days following the injury. These processes, which include alterations in cerebral blood flow and the pressure within the skull, contribute substantially to the damage from the initial injury. As a result brain function may be temporarily or permanently impaired and structural damage may or may not be detectable.

Deterioration in brain function and neurological functions of the brain can be attributed not only to the primary brain injury (the damage that occurs at the moment of trauma when tissues and blood vessels are stretched, compressed, and torn) but rather, to the secondary injury, expressed by a complex set of cellular processes and biochemical cascades that occur in the minutes to days following the trauma. These secondary processes can dramatically worsen the damage caused by primary injury and account for the greatest number of permannet imparment and also deaths. Secondary events include but are not limited to damage to the blood – brain barrier, release of factors that cause inflammation, free radical overload, excessive release of the neurotransmitter glutamate (excitotoxicity), influx of calcium and sodium ions into neurons, and dysfunction of mitochondria. Injured axons in the brain's white matter may separate from their cell bodies as a result of secondary injury, potentially killing those neurons. Other factors in secondary injury are changes in the blood flow to the brain; ischemia (insufficient blood flow); cerebral hypoxia (insufficient oxygen in the brain); cerebral edema (swelling of the brain); and raised intracranial pressure (the pressure within the skull). Intracranial pressure may rise due to swelling or a mass effect from a lesion, such as a hemorrhage. As a result, cerebral perfusion pressure (the pressure of blood flow in the brain) is reduced; ischemia results. When the pressure within the skull is too high, it can cause brain death or herniation, in which parts of the brain are squeezed by structures in the skull.

In another embodiment, a compound of the invention is utilized for use as a medicament.

In a further embodiment, a compound of the invention is used in the treatment of disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof. In one embodiment, a compound of the invention is used in the treatment of cerebral injury. In one embodiment said cerebral injury is selected from closed head injury, penetrating head injury, blast injury, cerebral ischemic-reperfusion injury, post-operable brain injury, brain hemorrhaging. In another embodiment a compound of the invention is utilized for use in lowering secondary damage produced by brain trauma.

In another one of its aspects the invention provides a pharmaceutical composition comprising a compound of the invention.

In one embodiment said pharmaceutical composition of the invention is for use in the treatment of disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof. In another embodiment said disease, disorder or condition is cerebral injury. In a further embodiment said cerebral injury is selected from closed head injury, penetrating head injury, blast injury, cerebral ischemic-reperfusion injury, post-operable brain injury, brain hemorrhaging. In another embodiment a pharmaceutical composition of the invention is used in lowering secondary damage produced by brain trauma.

In a further aspect of the invention, there is provided a use of a compound of the invention, for the manufacture of a pharmaceutical composition.

In some embodiments said p pharmaceutical composition is for use in the stimulation of bone growth, bone mass, bone repair or prevention of bone loss.

In another aspect, the invention provides a use of a compound of the invention, for the manufacture of a medicament (or pharmaceutical composition) capable of stimulating a CB receptor. In one embodiment receptor is a CB2 receptor.

In a further aspect the invention provides a use of a compound of the invention, for the manufacture of a medicament for the treatment of cerebral injury.

In another aspect the invention provides a use of a compound of the invention, for the manufacture of a medicament for lowering secondary damage produced by brain trauma.

In another one of its aspects the invention provides a use of a compound of the invention, for the preparation of a pharmaceutical composition for stimulation of bone growth, bone mass, bone repair or prevention of bone loss.

In a further aspect of the invention there is provided a compound of the invention, for use in the stimulation of bone growth, bone mass, bone repair or prevention of bone loss.

In another one of its aspects the invention provides a method of stimulation of bone growth, bone mass, bone repair or prevention of bone loss, said method comprising administering to a subject in need thereof a therapeutically effective amount of at least one compound of the invention.

In some embodiments said stimulation of bone growth, bone mass, bone repair or prevention of bone loss is associated with the treatment of at least one disease or a disorder selected from osteopenia, osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, osteoarthritis, periodontal disease or defect, an osteolytic bone loss disease, post-plastic surgery, post-orthopedic surgery, post oral surgery, post-orthopedic implantation, and post-dental implantation, primary and metastatic bone cancer, osteomyelitis, or any combinations thereof.

In other embodiments said at least one disease or disorder is selected from osteopenia and osteoporosis.

The term "*stimulation of bone growth, bone mass, bone repair*" is meant to encompass any quantitative and/or qualitative promotion of growth of the osseous tissue, any quantitative and/or qualitative promotion of mass of the osseous tissue and any quantitative and/or qualitative promotion of osseous tissue repair (for example in the case any part of the osseous tissue is damaged or fractured for example after impact or as a consequence of a disease, condition or any side effect of an external treatment) in vertebrates at any development stage (from embryonic stage to elderly). In some embodiments, the pharmaceutical composition is for increasing bone mass in a subject

in need thereof. In other embodiments, the pharmaceutical composition is for promoting bone repair.

The term *"prevention of bone loss"* is meant to encompass any quantitative and/or qualitative deterrence of osseous tissue loss in vertebrates at any development stage (from embryonic development stage to elderly).

Non-limiting examples of medical conditions benefiting from stimulating bone growth, gain of bone mass, prevention and rescue of bone loss and bone repair are osteopenia, osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, osteoarthritis, periodontal disease or defect, an osteolytic bone loss disease, post-plastic surgery, post-orthopedic surgery, post oral surgery, post-orthopedic implantation, and post-dental implantation, primary and metastatic bone cancer, osteomyelitis, or any combinations thereof. In some embodiments, a medical condition benefiting from stimulating bone growth is osteopenia or osteoporosis.

When referring to pharmaceutical compositions comprising a compound of the subject invention it should be understood to encompass admixtures of compounds of the invention, with pharmaceutically acceptable auxiliaries, and optionally other therapeutic agents. The auxiliaries must be "*acceptable*" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipients thereof.

Pharmaceutical compositions include those suitable for oral, rectal, nasal, topical (including transdermal, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration or administration via an implant. The compositions may be prepared by any method well known in the art of pharmacy. Such methods include the step of bringing in association compounds used in the invention or combinations thereof with any auxiliary agent.

Auxiliary agent(s), also named accessory ingredient(s), include those conventional in the art, such as carriers, fillers, binders, diluents, disintegrants, lubricants, colorants, flavouring agents, anti-oxidants, and wetting agents.

Pharmaceutical compositions suitable for oral administration may be presented as discrete dosage units such as pills, tablets, dragées or capsules, or as a powder or granules, or as a solution or suspension. The active ingredient may also be presented as a bolus or paste. The compositions can further be processed into a suppository or enema for rectal administration.

The invention further includes a pharmaceutical composition, as hereinbefore described, in combination with packaging material, including instructions for the use of the composition for a use as hereinbefore described.

For parenteral administration, suitable compositions include aqueous and non-aqueous sterile injection. The compositions may be presented in unit-dose or multi-dose containers, for example sealed vials and ampoules, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of sterile liquid carrier, for example water, prior to use.

For transdermal administration, e.g. gels, patches or sprays can be contemplated. Compositions or formulations suitable for pulmonary administration e.g. by nasal inhalation include fine dusts or mists which may be generated by means of metered dose pressurized aerosols, nebulisers or insufflators.

The exact dose and regimen of administration of the composition will necessarily be dependent upon the therapeutic or nutritional effect to be achieved and may vary with the particular formula, the route of administration, and the age and condition of the individual subject to whom the composition is to be administered.

In a further aspect the invention provides a method for stimulating a CB receptor in a subject in need thereof, said method comprising administering to said subject a therapeutically effective amount of a compound of the invention. In one embodiment said CB receptor is a CB2 receptor.

In another one of its aspects the invention provides a method of treating a disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof, said method comprising administering to in a subject in need thereof an effective amount of a compound of the invention.

In a further aspect the invention provides a method of treating cerebral injury in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound of the invention. In one embodiment said cerebral

injury is selected from closed head injury, penetrating head injury, blast injury, cerebral ischemic-reperfusion injury, post-operable brain injury, brain hemorrhaging.

In a further aspect the invention provides a method of lowering secondary damage produced by brain trauma in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound of the invention.

In a further aspect the invention provides a method of affecting the c-AMP formation in a subject in need thereof, said method comprising administering to said subject an effective amount of a compound of the invention.

When referring to the influence of a compound of the invention on the "*affecting the c-AMP formation*" it should be understood to encompass stimulation or inhibition of forskolin-induced c-AMP accumulation.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to understand the invention and to see how it may be carried out in practice, embodiments will now be described, by way of non-limiting example only, with reference to the accompanying drawings, in which:

Fig. 1A-1G show the GTPγS binding graphs for human CB2 receptor of compounds of the invention: HU-308 (Fig. 1A), HU-909 (Fig. 1B), HU-910 (Fig. 1C), HU-911 (Fig. 1D), HU-913 (Fig. 1E), HU-926 (Fig. 1F) and HU-928 (Fig. 1G). Data is shown as [^{35}S]GTPγS binding normalised to maximal HU-308 binding under the same experimental conditions.

Fig. 2 shows the extent of recovery (measured as ΔNSS (Neurological Severity Score)=NSS(1h)–NSS(t)) in a period of between 24h to 21days post closed head trauma (CHI) for groups receiving different doses of HU-910 (14b), (c1=0.1 mg/kg, c2=1 mg/kg, c3=10mg/kg, injected i.p. 1h after CHI). Control group (veh) received the vehicle alone (ethanol:cremophor:saline at ratio of 1:1:18).

Fig. 3 shows the extent of recovery (measured as ΔNSS (Neurological Severity Score)=NSS(1h)–NSS(t)) in a period of between 24h to 14day post closed head trauma (CHI) for groups receiving: 10mg/kg of HU-910 (14b) (injected i.p. 1h after CHI), 1mg/kg SR144528 CB2 antagonist alone, 1mg/kg SR144528 CB2 antagonist and 10mg/kg of HU-910 after 10 min. Control group (veh) received the vehicle alone (ethanol:cremophor:saline at ratio of 1:1:18).

Fig. 4 depicts the recovery of the four groups measured as ΔNSS (measured as ΔNSS (Neurological Severity Score)=NSS(1h)–NSS(t)), for a period of 1h to 28 days post CHI.

Fig. 5 depicts the Neurological Severity Score (ΔNSS=NSS(1h)–NSS(t)) was followed during 24h to 21 days post CHI.

Fig. 6 depicts the extent of recovery of the four groups (measured as ΔNSS= NSS(1h)–NSS(t), for a period of 24h to 28 day post CHI).

Fig. 7 depicts the Neurological Severity Score (NSS) as followed during 1h to 14 days post CHI.

Figs. 8A-8D depicts TNF-α production following CHI in left Cortex (Fig. 8A), left hippocampus (Fig. 8B), right Cortex (Fig. 8C) and right Hyppocampus (Fig. 8D).

DETAILED DESCRIPTION OF EMBODIMENTS

The following Examples are representative of techniques employed by the inventors in carrying out aspects of the present invention. It should be appreciated that while these techniques are exemplary of preferred embodiments for the practice of the invention, those of skill in the art, in light of the present disclosure, will recognize that numerous modifications can be made without departing from the spirit and intended scope of the invention.

EXAMPLE 1: SYNTHETIC PREPARATIONS

MATERIALS AND METHODS

All reagents were purchased from Sigma-Aldrich (Israel) and Acros (Israel) and used without further purification. (±)-Camphor and (+)-3-bromocamphor were purchased from Sigma-Aldrich (Israel). (±)-Camphor-10-sulfonyl chloride and (±)-camphorquinone were purchased from Acros (Israel).

All solvents were purchased from Bio-Lab (Israel).

All anhydrous reactions were performed under nitrogen atmosphere in flame-dried glassware using anhydrous solvents.

Silica gel 60Å 0.063-0.2 mesh was purchased from BioLab (Israel) and used for column chromatography.

Preparative thin layer chromatography (TLC) was performed on PLC silica gel plates 60 Å F_{254}, 2mm, purchased form Merck (Germany).

Purity of the intermediates and final compounds was established by analytical TLC on precoated aluminum silica gel 60, F_{254}, 200 μm, purchased from Merck (Germany) and chromatograms were visualized under ultraviolet light and by phosphomolybdic acid staining.

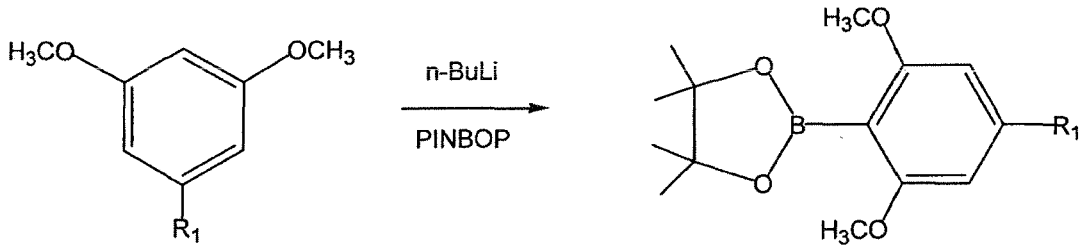
Melting points were determined on a capillary electrothermal melting point apparatus and are uncorrected.

^{1}H NMR spectra were recorded on Varian Unity Inova 300 MHz spectrometer and processed with the MestReC software. All NMR spectra were recorded using $CDCl_3$ as solvent unless otherwise stated and chemical shifts are reported in ppm relative to tetramethylsilane as internal standard. Multiplicities are indicated as s (singlet), d (doublet), dd (doblet of doublets), ddd (doublet of doublet of doublets), dddd (doublet of doublet of doublet of doublets), t (triplet), m (multiplet), and coupling constants (J) are reported in hertz (Hz).

Mass spectra were recorded on a Hewlett-Packard G2000 GC/MS system with HP-5971 gas chromatograph with an electron ionization detector.

Elemental analyses were performed on Perkin-Elmer 2400 series II Analyzer by Microanalytical Laboratory at the Department of Chemistry, Hebrew University of Jerusalem.

SYNTHETIC PREPARATIONS OF COMPOUNDS (3) AND (4):



1 - R_1: l',l'-dimethylheptyl

2 - R_1: n-pentyl

3- R_1: l',l'-dimethylheptyl(DMH)

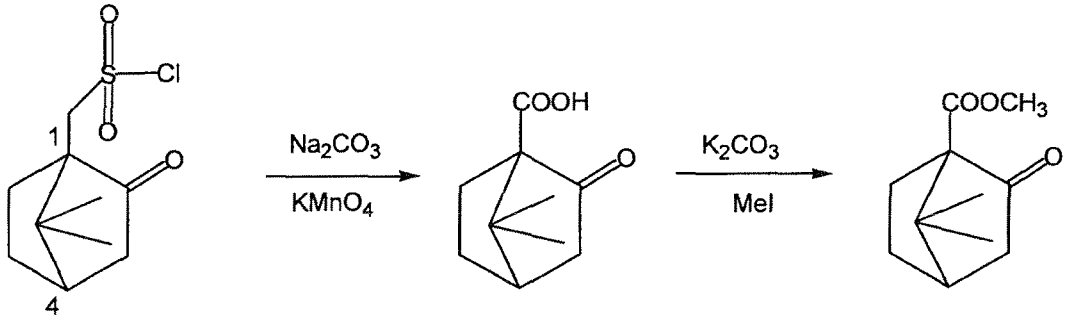
4- R_1: n-pentyl(C_5H_{11})

2-(2,6-dimethoxy-4-(2-methylheptan-2-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. (3). To a solution of 4-alkyl resorcinol dimethylether **1** 0.132 g (0.5 mmol) in 4 ml of THF *n*-BuLi 0.34 ml (0.55 mmol, 1.6 M solution in hexane) was added at 0°C. After additional stirring for 1 h at 0°C, the reaction mixture was cooled to -78°C and a solution of PINBOP 0.15 ml (0.75 mmol) was added all at once. The

reaction mixture was allowed to warm up to the room temperature and continued to stir overnight. The reaction worked up with aqueous NH_4Cl, extracted with 3 portions of diethyl ether which washed with brine and water. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The product was obtained as a non-separable mixture of pinacol aryl boronate **3** and 4-alkyl resorcinol dimethylether **1** (in ratio 4:3 according to GC-MS analysis) 0.19 g and was used as it is in Suzuki coupling reaction. The ^1H NMR (300 MHz, *CDCl3*) δ ppm 6.41 (s, 2H), 3.76 (s, 6H), 1.51-1.58 (m, 2H), 1.37 (s, 6H), 1.25 (s, 6H), 1.24 (s, 6H), 1.13-1.21 (m, 8H), 0.84 (t, J = 6.87 Hz, 3H). Exact mass calculated for $C_{27}H_{34}O_3$ m/e 390.29; found 390.80.

2-(2,6-dimethoxy-4-pentylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4). The title compound was prepared by the general procedure described for compound **3**, using 4-alkyl resorcinol dimethylether **2** 0.104 g (0.5 mmol) in 4 ml of THF, *n*-BuLi 0.34 ml (0.55 mmol, 1.6 M solution in hexane) and PINBOP 0.15 ml (0.75 mmol). The product was obtained as a non-separable mixture 0.165 g of pinacol aryl boronate **4** and 4-alkyl resorcinol dimethylether **2** (in ratio 4:3 according to GC-MS analysis) and was used as it is in Suzuki coupling reaction. ^1H NMR (300 MHz, *CDCl3*) δ ppm 6.28 (s, 2H), 3.76 (s, 6H), 2.55 (t, J =7.53 Hz, 2H), 1.55-1.63 (m, 2H), 1.27 (s, 6H), 1.26 (s, 6H), 1.24 (m, 4H), 0.87 (m, 3H). Exact mass calculated for $C_{27}H_{34}O_3$ m/e 334.23; found 334.62.

SYNTHETIC PREPARATIONS OF COMPOUND (7):



5a-(1R,4S)
5b-(1S,4R)

6a-(1R,4S)
6b-(1S,4R)

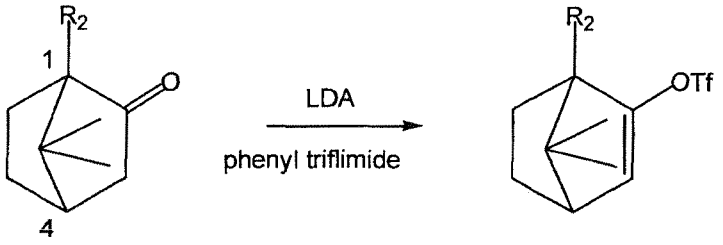
7a-(1R,4S)
7b-(1S,4R)

(1R,4S)-methyl-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylate (7a) To a mixture of ketopinic acid **6a** 0.182 g (1 mmol) and K_2CO_3 1.1 g (8 mmol) stirred in DMF 10 ml was added MeI 0.125 ml (0.284 g, 2 mmol). The reaction mixture was

allowed to stir for 18 hrs at ambient temperature. The reaction mixture was dissolved in water 80 ml and extracted with 3×30 ml portions of diethyl ether. The organic phase was washed with $NaHCO_3$ saturated solution, dried over $MgSO_4$ and concentrated in vacuo to give yellow oil 0.184 g (94%). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 3.75 (s, 3H), 2.53 (ddd, J = 18.29, 3.7 Hz, 1H), 2.36 (ddd, J = 14.99, 11.82, 3.99 Hz, 1H), 2.10 (t, J = 4.4 Hz, 1H), 2.02 (m, 1H), 1.92-1.98 (d, J = 18.40 Hz, 1H), 1.79 (ddd, J = 14.16, 9.35, 4.95 Hz, 1H), 1.41 (ddd, J = 12.65, 9.49, 4.26 Hz, 1H), 1.15 (s, 3H), 1.07 (s, 3H). Exact mass calculated for $C_{11}H_{16}O_3$ m/e 196.11; found 196.22.

(1S,4R)-methyl-7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylate (7b) The title compound was prepared from **6b** by the general procedure described for compound **7a**. Yellow oil (96%). ^1H NMR (300 MHz, $CDCl_3$) δ ppm 3.75 (s, 3H), 2.53 (ddd, J = 18.29, 3.7 Hz, 1H), 2.36 (ddd, J = 14.99, 11.82, 3.99 Hz, 1H), 2.10 (t, J = 4.4 Hz, 1H), 2.02 (m, 1H), 1.92-1.98 (d, J = 18.40 Hz, 1H), 1.79 (ddd, J = 14.16, 9.35, 4.95 Hz, 1H), 1.41 (ddd, J = 12.65, 9.49, 4.26 Hz, 1H), 1.15 (s, 3H), 1.07 (s, 3H). Exact mass calculated for $C_{11}H_{16}O_3$ m/e 196.11; found 196.22.

SYNTHETIC PREPARATIONS OF COMPOUNDS (9) AND (10):



7a-(1R,4S); R2:$COOCH_3$ **9a**-(1R,4S); R2:$COOCH_3$

7b-(1S,4R); R2:$COOCH_3$ **9b**-(1S,4R); R2:$COOCH_3$

8a-(1R,4R); R_2:CH_3 **10a**-(1R,4R); R_2:CH_3

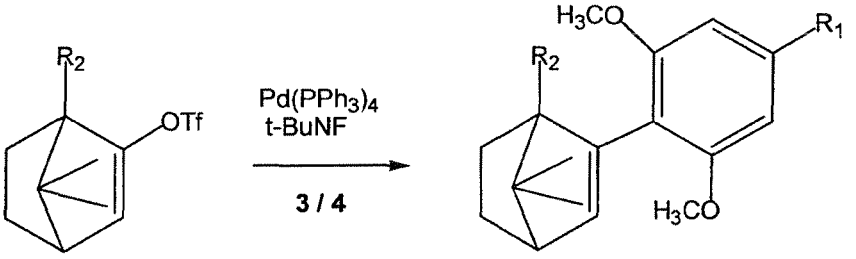
8b-(1S,4S); R_2:CH_3 **10b**-(1S,4S); R_2:CH_3

(1R,4S)-methyl-7,7-dimethyl-2-(trifluoromethylsulfonyloxy)bicyclo[2.2.1]hept-2-ene-1-carboxylate (9a) Precooled (0°C) solution of methyl ester **7a** 0.06 g (0.3 mmol) in 1.5 ml THF was added to a solution of LDA 0.17 ml (0.34 mmol, 2M solution) in 2 ml THF at -78°C and resultant solution was allowed to stir for 2 hrs. A solution of phenyl triflimide 0.115 g (0.32 mmol) in 2 ml of THF was added, and the reaction was stirred at 0°C for 3 hrs and was allowed to stir for additional 15 hrs at room temperature. After the solvent removal at

the rotary evaporator, the resultant, yellow oil was purified by silica gel chromatography (petroleum ether/ether) to give brownish oil 0.07 g (71%). ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 5.81 (d, *J* =3.74, 1H), 3.77 (s, 3H), 2.51 (t, *J* = 3.67 Hz, 1H), 2.39 (ddd, *J* = 3.71, 8.76, 12.47 Hz, 1H), 2.03-2.13 (m, 1H), 1.65 (ddd, *J* = 3.68, 9.18, 12.65 Hz, 1H), 1.24 (ddd, *J* = 3.72, 9.18, 12.64 Hz, 1H), 1.11(s, 3H), 0.97 (s, 3H). Exact mass calculated for $C_{12}H_{15}F_3O_5S$ m/e 328.06; found 328.44.

(1S,4R)-methyl-7,7-dimethyl-2-(trifluoromethylsulfonyloxy)bicyclo[2.2.1]hept-2-ene-1-carboxylate (9b) The title compound was prepared from **7b** by the general procedure described for compound **9a**. Brownish oil (68%). ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 5.81 (d, *J* =3.74, 1H), 3.77 (s, 3H), 2.51 (dd, *J* = 3.67, 3.67 Hz, 1H), 2.39 (ddd, *J* = 3.71, 8.76, 12.47 Hz, 1H), 2.03-2.13 (m, 1H), 1.65 (ddd, *J* = 3.68, 9.18, 12.65 Hz, 1H), 1.24 (ddd, *J* = 3.72, 9.18, 12.64 Hz, 1H), 1.11(s, 3H), 0.97 (s, 3H). Exact mass calculated for $C_{12}H_{15}F_3O_5S$ m/e 328.06; found 328.44.

SYNTHETIC PREPARATIONS OF COMPOUNDS (11), (12) AND (13):



9a-(1R,4S); R2:$COOCH_3$
9b-(1S,4R); R2:$COOCH_3$
10a-(1R,4R); R_2:CH_3
10b-(1S,4S); R_2:CH_3

11a-(1R,4S); R_1:DMH; R_2:$COOCH_3$
11b-(1S,4R); R_1:DMH; R_2:$COOCH_3$
12a-(1R,4R); R_1:DMH; R_2:CH_3
12b-(1S,4S); R_1:DMH; R_2:CH_3
13a-(1R,4S); R_1:C_5H_{11}; R_2:$COOCH_3$
13b-(1S,4R); R_1:C_5H_{11}; R_2:$COOCH_3$

(1R,4S)-methyl-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate (11a) A pinacol arylboronate **3** (mixed with 4-alkyl resorcinol dimethylether **1**) 0.474 g, enol triflate **9a** 0.328 g (1.00 mmol), $Pd(PPh_3)_4$ 0.07 g (0.006mmol) and t-BuNF 1.5 ml (1.5 mmol, 1M solution in THF) in THF 15 ml were refluxed for 15 hrs. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. Further purification by silica gel

column chromatography (petroleum ether/ ether) afforded a desired product as pale yellow oil 0.288 g (65%). ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.45 (s, 2H), 6.28 (d, *J* = 3.42 Hz, 1H), 3.72 (s, 6H), 3.45 (s, 3H), 2.43 (m, 2H), 1.80-2.03 (m, 1H), 1.53-1.58 (m, 2H), 1.26 (s, 6H), 1.13-1.22 (m, 7H), 1.11 (s, 3H), 0.98-1.08 (m, 3H), 0.97 (s, 3H), 0.84 (t, *J* = 6.79 Hz, 3H). Exact mass calculated for $C_{28}H_{42}O_4$ m/e 442.31; found 442.92. Anal. calcd. for $C_{28}H_{42}O_4$: C, 75.98; H, 9.56. Found: C, 76.14; H, 9.65.

(1S,4R)-methyl-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate (11b, HU-912) The title compound was prepared from **9b** by the general procedure described for compound **11a**. Yellowish oil (69%). ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.45 (s, 2H), 6.28 (d, *J* = 3.42 Hz, 1H), 3.72 (s, 6H), 3.45 (s, 3H), 2.43 (m, 2H), 1.80-2.03 (m, 1H), 1.53-1.58 (m, 2H), 1.26 (s, 6H), 1.13-1.22 (m, 7H), 1.11 (s, 3H), 0.98-1.08 (m, 3H), 0.97 (s, 3H), 0.84 (t, *J* = 6.79 Hz, 3H). Exact mass calculated for $C_{28}H_{42}O_4$ m/e 442.31; found 442.91. Anal. calcd. for $C_{28}H_{42}O_4$: C, 75.98; H, 9.56. Found: C, 75.58; H, 9.70.

(1R,4S)-methyl-2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate (13a, HU-971) The title compound was prepared by the general procedure described for compound **11a (HU-911)**, using pinacol arylboronate **4** (mixed with **2)** 0.244 g, enol triflate **9a** 0.2 g (0.61 mmol), $Pd(PPh_3)_4$ 0.042 g (0.037 mmol) and t-BuNF 0.91 ml (0.91 mmol, 1M solution in THF) to give colorless oil 170 mg (72%). ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.33 (s, 2H), 6.26 (d, *J* = 3.42 Hz, 1H), 3.71 (s, 6H), 3.47 (s, 3H), 2.55 (t, *J* = 7.70 Hz, 2H), 2.38-2.46 (m, 2H), 1.81-2.03 (m, 2H), 1.56-1.66 (m, 2H), 1.30-1.35 (m, 4H), 1.12 (s, 3H, syn), 1.07-1.16 (m, 1H), 0.97 (s, 3H, anti), 0.90 (t, *J* = 6.84 Hz, 3H). Exact mass calculated for $C_{24}H_{34}O_4$ by the general procedure described for compo$_4O_4$: C, 74.58; H, 8.87. Found : C, 74.61; H, 9.04.

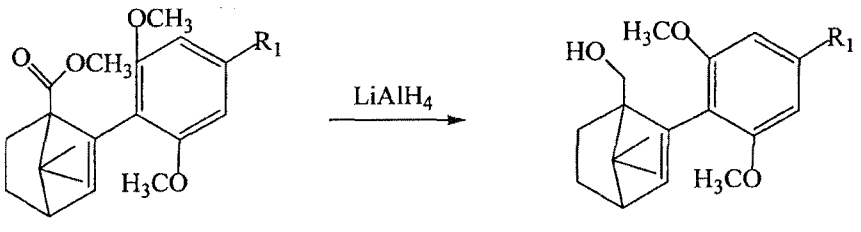
(1S,4R)-methyl-2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylate (13b, HU-972). The title compound was prepared from **9b** by the general procedure described for compound **13a (HU-971)**. Colorless oil (69%). ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.33 (s, 2H), 6.26 (d, *J* = 3.42 Hz, 1H), 3.71 (s, 6H), 3.47 (s, 3H), 2.55 (t, *J* = 7.70 Hz, 2H), 2.38-2.46 (m, 2H), 1.81-2.03 (m, 2H), 1.56-1.66 (m, 2H), 1.30-1.35 (m, 4H), 1.12 (s, 3H, syn), 1.07-1.16 (m, 1H), 0.97 (s, 3H, anti), 0.90 (t, *J* = 6.84 Hz, 3H). Exact mass calculated for $C_{24}H_{34}O_4$

m/e 386.25; found 386.67. Anal. calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.31; H, 8.90.

(1R,4R)-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (12a, HU-907). The title compound was prepared by the general procedure described for compound **11a,** using pinacol arylboronate **3** (mixed with **1**) 0.755 g, camphor enol triflate **10a** 0.5 g (1.76 mmol), $Pd(PPh_3)_4$ 0.122 g (0.011 mmol) and t-BuNF 2.64 ml (2.64 mmol, 1M solution in THF) to give yellowish oil 0.525 g (75%), which solidified upon standing at -20°C to give a white solid. mp 34-36°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.50 (s, 2H), 5.87 (d, *J* = 3.27 Hz, 1H), 3.74 (s, 6H), 2.37 (t, *J* = 3.46, 1H), 1.88 (m, 1H), 1.65 (m, 1H), 1.61 (m, 2H), 1.55 (m, 1H), 1.30 (s, 6H), 1.15 (m, 1H), 1.19-1.26 (m, 6H), 1.07-1.18 (m, 2H), 1.05 (s, 3H), 0.86 (t, *J* = 6.71 Hz, 3H), 0.83 (s, 3H), 0.82 (s, 3H). Exact mass calculated for $C_{27}H_{42}O_2$ m/e 398.32; found 398.79. Anal. calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.08; H, 10.69.

(1S,4S)-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (12b, HU-908). The title compound was prepared from **10b** by the general procedure described for compound **12a (HU-907).** White solid (81%). mp 35-37°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.50 (s, 2H), 5.87 (d, *J* = 3.27 Hz, 1H), 3.74 (s, 6H), 2.37 (t, *J* = 3.46, 1H), 1.88 (m, 1H), 1.65 (m, 1H), 1.61 (m, 2H), 1.55 (m, 1H), 1.30 (s, 6H), 1.15 (m, 1H), 1.19-1.26 (m, 6H), 1.07-1.18 (m, 2H), 1.05 (s, 3H), 0.86 (t, *J* = 6.71 Hz, 3H), 0.83 (s, 3H), 0.82 (s, 3H). Exact mass calculated for $C_{27}H_{42}O_2$ m/e 398.32; found 398.79. Anal. calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.47; H, 10.85.

SYNTHETIC PREPARATIONS OF COMPOUNDS (14) AND (15):



11a-(1R,4S); R_1:DMH
11b-(1S,4R); R_1:DMH
13a-(1R,4S); R_1:C_5H_{11}
13b-(1S,4R); R_1:C_5H_{11}

14a-(1R,4S); R_1:DMH
14b-(1S,4R); R_1:DMH
15a-(1R,4S); R_1:C_5H_{11}
15b-(1S,4R); R_1:C_5H_{11}

(1R,4S)-(2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol (14a, HU-909). Solution of methyl ester **11a** 0.790 g (1.79 mmol) in THF 20 ml was cooled to 0°C. After addition of $LiAlH_4$ 3.58 ml (3.58 mmol, 1M solution in diethyl ether) the reaction was allowed to warm up to ambient temperature and stirred for 18 hrs. The reaction worked up with a small amount of saturated $MgSO_4$ solution and extracted with ethyl acetate. The organic phase was washed with brine and water, dried over $MgSO_4$ and concentrated in vacuo. The product was purified by silica gel column chromatography (petroleum ether/ ether) to give oil 0.460 g (62%), which solidified upon standing at -20°C to give a yellow solid. mp 49-51°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.52 (s, 2H), 5.90 (d, *J* = 3.24 Hz, 1H), 3.75 (s, 6H), 3.65 (m, 2H), 2.35 (t, *J* = 3.39, 1H), 2.25 (*dd, J* = 7.29, *J* = 5.01,1H), 1.93 (m, 1H), 1.53-1.59 (m, 5H), 1.27 (s, 6H), 1.21 (s, 3H), 1.0-1.19 (m, 7H), 0.94 (s, 3H), 0.85 (t, *J* = 6.71 Hz, 3H). Exact mass calculated for $C_{27}H_{42}O_3$ m/e 414.31; found 414.87. Anal. calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.31; H, 10.31.

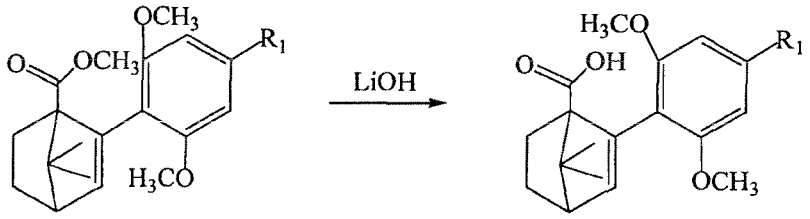
(1S,4R)-(2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol (14b, HU-910). The title compound was prepared from **11b (HU-912)** by the general procedure described for compound **14a (HU-909).** White solid (64%). mp 48-50°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.52 (s, 2H), 5.90 (d, *J* = 3.24 Hz, 1H), 3.75 (s, 6H), 3.65 (m, 2H), 2.35 (t, *J* = 3.39, 1H), 2.25 (*dd, J* = 7.29, *J* = 5.01,1H), 1.93 (m, 1H), 1.53-1.59 (m, 5H), 1.27 (s, 6H), 1.21 (s, 3H), 1.0-1.19 (m, 7H), 0.94 (s, 3H), 0.85 (t, *J* = 6.71 Hz, 3H). Exact mass calculated for $C_{27}H_{42}O_3$ m/e 414.31; found 414.86. Anal. calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.08; H, 10.32.

(1R,4S)-(2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol (15a, HU-969). The title compound was prepared by the general procedure described for compound **14a (HU-909)**, using methyl ester **13a (HU-971)** 0.1 g (0.259 mmol) in 3 ml of dry THF and $LiAlH_4$ 0.51 ml (0.518 mmol, 1M solution in diethyl ether). The product was purified by silica gel column chromatography (petroleum ether/ether) to give oil 0.086 g (93%), which solidified upon standing at -20°C to give a white solid. mp 28-29°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.40 (s, 2H), 5.88 (d, *J* = 3.24 Hz, 1H), 3.74 (s, 6H), 3.65 (d, *J* = 2.51 Hz, 2H), 2.58 (t, *J* = 7.70 Hz, 2H), 2.35 (t, *J* = 3.41 Hz, 1H), 1.89-1.98 (m, 1H), 1.54-1.66 (m, 4H), 1.32-1.38 (m,

4H), 1.23 (s, 3H), 1.11-1.19 (m, 1H), 0.94 (s, 3H), 0.92 (t, J = 6.84 Hz, 3H). Exact mass calculated for $C_{23}H_{34}O_3$ m/e 358.25; found 358.67. Anal. calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.06; H, 9.72.

(1S,4R)-(2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-1-yl)methanol (15b, HU-970). The title compound was prepared from **10b** by the general procedure described for compound **13b (HU-972).** Oil (83%), which solidified upon standing at -20°C. mp 26-27°C;^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.40 (s, 2H), 5.88 (d, J = 3.24 Hz, 1H), 3.74 (s, 6H), 3.65 (d, J = 2.51 Hz, 2H), 2.58 (t, J = 7.70 Hz, 2H), 2.35 (t, J = 3.41 Hz, 1H), 1.89-1.98 (m, 1H), 1.54-1.66 (m, 4H), 1.32-1.38 (m, 4H), 1.23 (s, 3H), 1.11-1.19 (m, 1H), 0.94 (s, 3H), 0.92 (t, J = 6.84 Hz, 3H). Exact mass calculated for $C_{23}H_{34}O_3$ m/e 358.25; found 358.71. Anal. calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.25; H, 9.55.

SYNTHETIC PREPARATIONS OF COMPOUNDS (16) AND (17):



11a-(1R,4S); R_1:DMH
11b-(1S,4R); R_1:DMH
13a-(1R,4S); R_1:C_5H_{11}
13b-(1S,4R); R_1:C_5H_{11}

16a-(1R,4S); R_1:DMH
16b-(1S,4R); R_1:DMH
17a-(1R,4S); R_1:C_5H_{11}
17b-(1S,4R); R_1:C_5H_{11}

(1R,4S)-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid (16a, HU-913). Methyl ester **11a (HU-911)** 0.103 g (0.233 mmol) and LiOH 0.111 g (4.66 mmol) in 2 ml of MeOH/H_2O 3:1 were heated at 200°C over 48 hrs in a screwed vial under air atmosphere. Water was added to the reaction mixture and extracted several times with ether. Organic phases were collected, dried over $MgSO_4$ and concentrated in vacuo. The product was purified by preparative TLC (hexane/ethyl acetate) to give yellow solid 0.026 g (26%). mp 101-102°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.46 (s, 2H), 6.32 (d, J = 3.40 Hz, 1H), 3.71 (s, 6H), 2.46 (t, J = 3.44 Hz, 1H), 2.38-2.44 (m, 1H), 1.80-2.03 (m, 1H), 1.53-1.58 (m, 2H), 1.26 (s, 6H), 1.16-1.24 (m, 7H), 1.14 (s, 3H), 1.03-1.12 (m, 3H), 1.00 (s, 3H),

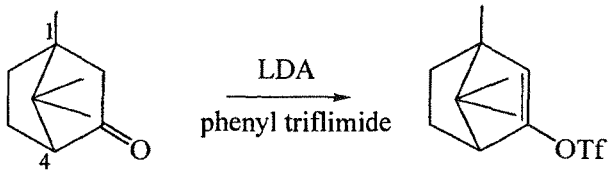
0.85 (t, J = 6.74 Hz, 3H). Exact mass calculated for $C_{28}H_{42}O_4$ m/e 428.29; found 428.98. Anal. calcd. for $C_{28}H_{42}O_4$: C, 75.66; H, 9.41. Found: C, 75.50; H, 9.48.

(1S,4R)-2-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid (16b, HU-914). The title compound was prepared from **11b (HU-912)** by the general procedure described for compound **16a (HU-913).** Yellow solid (25%). mp 100-101°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.46 (s, 2H), 6.32 (d, J = 3.40 Hz, 1H), 3.71 (s, 6H), 2.46 (t, J = 3.44 Hz, 1H), 2.38-2.44 (m, 1H), 1.80-2.03 (m, 1H), 1.53-1.58 (m, 2H), 1.26 (s, 6H), 1.16-1.24 (m, 7H), 1.14 (s, 3H), 1.03-1.12 (m, 3H), 1.00 (s, 3H), 0.85 (t, J = 6.74 Hz, 3H). Exact mass calculated for $C_{28}H_{42}O_4$ m/e 428.29; found 428.98. Anal. calcd. for $C_{28}H_{42}O_4$: C, 75.66; H, 9.41. Found: C, 74.81; H, 9.40.

(1R,4S)-2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid (17a, HU-973). The title compound was prepared by the general procedure described for compound **16a (HU-913)**, using methyl ester **13a (HU-971)** 0.075 g (0.194 mmol) and LiOH 0.093 g (3.89 mmol) in 1.5 ml of MeOH/H_2O 3:1. The product was purified by preparative TLC (hexane/ethyl acetate) to give yellowish solid 0.010 g (14%). mp 85-87°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.33 (s, 2H), 6.28 (d, J = 3.39 Hz, 1H), 3.69 (s, 6H), 2.55 (t, J = 7.80 Hz, 2H), 2.45 (t, J = 3.48 Hz, 1H), 2.36-2.44 (m, 1H), 1.82-2.03 (m, 2H), 1.55-1.65 (m, 2H), 1.30-1.35 (m, 4H), 1.14 (s, 3H), 1.06-1.12 (m, 1H), 1.00 (s, 3H), 0.90 (t, J = 6.84 Hz, 3H). Exact mass calculated for $C_{23}H_{32}O_4$ m/e 372.23; found 372.92. Anal. calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.91; H, 8.80.

(1S,4R)-2-(2,6-dimethoxy-4-pentylphenyl)-7,7-dimethylbicyclo[2.2.1]hept-2-ene-1-carboxylic acid (17b, HU-974). The title compound was prepared from **13b (HU-972)** by the general procedure described for compound **17a (HU-973).** Yellowish solid (21%). mp 84-86°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.33 (s, 2H), 6.28 (d, J = 3.39 Hz, 1H), 3.69 (s, 6H), 2.55 (t, J = 7.80 Hz, 2H), 2.45 (t, J = 3.48 Hz, 1H), 2.36-2.44 (m, 1H), 1.82-2.03 (m, 2H), 1.55-1.65 (m, 2H), 1.30-1.35 (m, 4H), 1.14 (s, 3H), 1.06-1.12 (m, 1H), 1.00 (s, 3H), 0.90 (t, J = 6.84 Hz, 3H). Exact mass calculated for $C_{23}H_{32}O_4$ m/e 372.23; found 372.92. Anal. calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.60; H, 8.70.

SYNTHETIC PREPARATIONS OF COMPOUND (19):



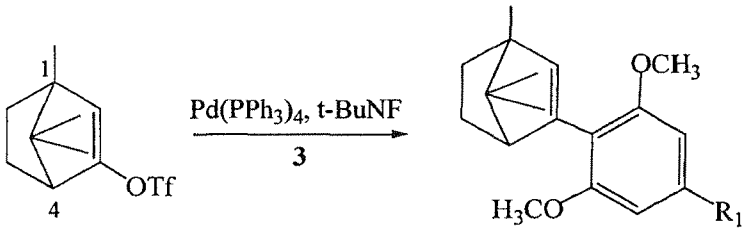
18a-(1S,4S)
18b-(1R,4R)

19a-(1S,4S)
19b-(1R,4R)

(1S,4S)-4,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl trifluoromethanesulfonate (19a). The title compound was prepared by the general procedure described for compound **9a**, using ketone **18a** 0.375 g (2.35 mmol), LDA 1.29 ml (2.58 mmol, 2M solution) and phenyl triflimide 0.943 g (2.64mmol). The product was purified by silica gel column chromatography (petroleum ether/ ether) to give oil 0.514 g (77%). ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 5.37 (d, J=1.04 Hz, 1H), 2.45 (d, *J* = 3.48 Hz, 1H), 1.93 (dddd, *J* = 3.43, 3.43, 7.85, 11.61 Hz, 1H), 1.70 (ddd, *J* = 3.12, 8.52, 11.84 Hz, 1H), 1.19-1.38 (m, 2H), 1.08 (s, 3H), 0.97 (s, 3H), 0.78 (s, 3H). Exact mass calculated for $C_{11}H_{15}F_3O_3S$, 284.07, found, 284.77.

(1R,4R)-4,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl trifluoromethanesulfonate (19b). The title compound was prepared from **18b** by the general procedure described for compound **19a.** Brownish oil (73%). ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 5.37 (d, J=1.04 Hz, 1H), 2.45 (d, *J* = 3.48 Hz, 1H), 1.93 (dddd, *J* = 3.43, 3.43, 7.85, 11.61 Hz, 1H), 1.70 (ddd, *J* = 3.12, 8.52, 11.84 Hz, 1H), 1.19-1.38 (m, 2H), 1.08 (s, 3H), 0.97 (s, 3H), 0.78 (s, 3H). Exact mass calculated for $C_{11}H_{15}F_3O_3S$, 284.07, found, 284.77.

SYNTHETIC PREPARATIONS OF COMPOUND (20):



19a-(1S,4S)
19b-(1R,4R)

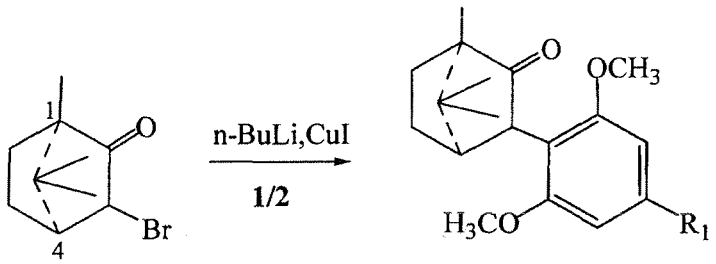
20a-(1S,4S); R1:DMH
20b-(1R,4R); R1:DMH

(1S,4S)-3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (20a, HU-917). The title compound was prepared

by the general procedure described for compound **11a (HU-911)**, using pinacol arylboronate **3** (mixed with 4-alkyl resorcinol dimethylether **1)** 0.755 g, enol triflate **19a** 0.17 g (0.598 mmol), $Pd(PPh_3)_4$ 0.041 g (0.036 mmol) and t-BuNF 0.9 ml (0.9 mmol, 1M solution in THF). The product was purified by silica gel column chromatography (petroleum ether/ ether) to give oil 0.185 g (78%), which solidified upon standing at -20°C. mp 33-34°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.50 (s, 2H), 5.79 (d, *J* = 3.00 Hz, 1H), 3.76 (s, 6H), 2.60 (d, *J* = 3.51, 1H), 1.81 (m, 1H), 1.64 (m, 1H), 1.60 (m, 1H), 1.55 (m, 2H), 1.31 (m, 1H), 1.28 (s, 6H), 1.17-1.25 (m, 8H), 1.08 (s, 3H), 0.99 (s, 3H), 0.86 (t, *J* = 6.69 Hz, 3H), 0.81 (s, 3H). Exact mass calculated for $C_{27}H_{42}O_2$ m/e 398.32; found 398.82. Anal. calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.50; H, 10.71.

(1R,4R)-3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (20b, HU-918). The title compound was prepared from **19b** by the general procedure described for compound **20a (HU-917).** Yellowish solid (77%). mp 32-33°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.50 (s, 2H), 5.79 (d, *J* = 3.00 Hz, 1H), 3.76 (s, 6H), 2.60 (d, *J* = 3.51, 1H), 1.81 (m, 1H), 1.64 (m, 1H), 1.60 (m, 1H), 1.55 (m, 2H), 1.31 (m, 1H), 1.28 (s, 6H), 1.17-1.25 (m, 8H), 1.08 (s, 3H), 0.99 (s, 3H), 0.86 (t, *J* = 6.69 Hz, 3H), 0.81 (s, 3H). Exact mass calculated for $C_{27}H_{42}O_2$ m/e 398.32; found 398.84. Anal. calcd. for $C_{27}H_{42}O_2$: C, 81.35; H, 10.62. Found: C, 81.56; H, 10.85.

SYNTHETIC PREPARATIONS OF COMPOUNDS (22, HU-936) AND (23, HU-926):



21-(1R,4S)

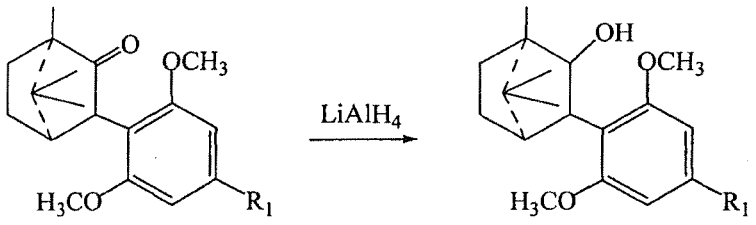
22 - R_1:C_5H_{11}
23 - R_1:DMH

(1R,4R)-3-(2,6-dimethoxy-4-pentylphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (22, HU-936). n-BuLi 0.6 ml (0.96 mmol, 1.6 M in hexanes) was added to a precooled (0°C) solution of **2** 0.2g (0.96 mmol) in 3 ml of diethyl ether. The resulting solution was allowed to stir for 2.5 hrs at room temperature. The solution was then cooled back to 0°C and transferred dropwise via cannula to a

suspension of CuI 0.092 g (0.48 mmol) in 2 ml of diethyl ether at 0°C. The resulting solution was allowed to stir for 30 min and 5 ml of anhydrous DMSO was added. Then the solution of 3-bromocamphor **21** 0.086g (0.37 mmol) in 1ml of diethyl ether and 1 ml of DMSO at 0°C was added dropwise via septum. The reaction was then allowed to warm to room temperature and stirred over 15 hrs. The reaction was quenched by the addition of 5 ml of saturated aqueous NH_4Cl. The water phase was extracted three times with diethyl ether. The combined organic layers were washed three times with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. Further purification by silica gel column chromatography (petroleum ether/ ether) afforded white crystals of **22 (HU-936)** 0.093g (70%). mp 62°C; ^{1}H NMR (300 MHz, *CDCl*$_3$) δ ppm 6.37 (s, 2H), 3.89 (d, *J*=4.23 Hz, 1H), 3.72 (s, 6H), 2.55 (t, *J*=7.87 Hz, 2H), 2.19 (t, *J*=4.11Hz, 1H), 1.71-1.76 (m, 2H), 1.63 (m, 1H), 1.59 (m, 2H), 1.37 (m, 1H), 1.33-1.36 (m, 4H), 1.02 (s, 3H), 1.002 (s, 3H), 0.97 (s, 3H), 0.91 (t, *J*=6.93 Hz, 3H). Exact mass calculated for $C_{23}H_{34}O_3$ m/e 358.25; found 358.67. Anal. calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.20; H, 9.63.

(1R,4R)-3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (23, HU-926). The title compound was prepared by the general procedure described for compound **22 (HU-936)**, using **1** 0.23g (0.87 mmol), n-BuLi 0.54ml (0.87 mmol, 1.6 M in hexanes), CuI 0.083g (0.44 mmol), 3-bromocamphor **21** 0.069g (0.3 mmol). Further purification by silica gel column chromatography (petroleum ether/ ether) afforded white crystals of **23 (HU-926)** 0.081g (65%). mp 64-65°C; ^{1}H NMR (300 MHz, *CDCl*$_3$) δ ppm 6.49 (s, 2H), 3.89 (d, *J*=4.23 Hz, 1H), 3.72 (s, 6H), 2.19 (t, *J*=4.11 Hz, 1H), 1.71-1.76 (m, 1H), 1.53-1.68 (m, 4H), 1.30-1.42 (m, 1H), 1.26 (s, 6H), 1.15-1.24 (m, 8H), 1.01 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H), 0.85 (t, *J*=6.73 Hz, 3H). Exact mass calculated for $C_{27}H_{42}O_3$ m/e 414.31; found 414.84. Anal. calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.39; H, 10.27.

SYNTHETIC PREPARATIONS OF COMPOUNDS (24, HU-938) AND (25, HU-928):



22 - R_1:C_5H_{11}
23 - R_1:DMH

24 - R_1:C_5H_{11}
25 - R_1:DMH

(1R,4R)-3-(2,6-dimethoxy-4-pentylphenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (24, HU-938). Ketone **22 (HU-936)** 0.085g (0.23 mmol) in 1 ml of diethyl ether was added to a precooled (0°C) solution of $LiAlH_4$ 0.14 ml (0.14 mmol, 1M solution in diethyl ether) in diethyl ether 2 ml. After stirring under reflux for 1h the reaction mixture was cooled to 0°C and quenched by addition of EtOAc.

Water was added to the reaction mixture and it was extracted with 3 portions of diethyl ether, followed by washing with aqueous HCl 10%. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. Further purification by silica gel column chromatography (ether/petroleum ether) afforded white crystals of **24 (HU-938)** 0.078 g (92%). mp 58-60°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.44 (s, 2H), 4.52 (d, *J*=6.96 Hz, *J*=1.87 Hz, 1H), 4.14-4.17 (m, 2H), 3.82 (s, 6H), 2.56 (t, *J*=7.70 Hz, 2H), 2.19 (t, *J*=4.11Hz, 1H), 1.77-1.89 (m, 2H), 1.63 (m, 1H), 1.46-1.70 (m, 3H), 1.23-1.41 (m, 4H), 1.06 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.90 (t, *J*=6.93 Hz, 3H,). Exact mass calculated for $C_{23}H_{36}O_3$ m/e 360.27; found 360.65. Anal. calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.46; H, 10.11.

(1R,4R)-3-(2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (25, HU-928). The title compound was prepared by the general procedure described for compound **24 (HU-938)**, using ketone **23 (HU-926)** 0.238 g (0.57 mmol), $LiAlH_4$ 0.345 ml (0.34 mmol).Further purification by silica gel column chromatography (ether/petroleum ether) afforded white crystals of **25 (HU-928)** 0.208 g (88%). mp 96-98°C; ^{1}H NMR (300 MHz, *CDCl$_3$*) δ ppm 6.55 (s, 2H), 4.58 (dd, *J*=8.88 Hz, 1H), 4.14-4.17 (m, 2H), 3.82 (s, 6H), 1.78-1.88 (m, 2H), 1.48-1.61 (m, 5H), 1.29-1.33 (m, 1H), 1.27 (s, 6H), 1.16-1.25 (m, 7H), 1.06 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H), 0.85 (t, *J*=6.74 Hz, 3H). Exact mass calculated for $C_{27}H_{44}O_3$ m/e 416.33; found 416.90. Anal. calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.64. Found: C, 78.10; H, 10.82.

EXAMPLE 2: *IN VITRO* BINDING TO CANNABINOID RECEPTORS

CELL LINE GENERATION AND MAINTENANCE

The cDNA clones for human HA- tagged CB1 and CB2 receptors were obtained from the Missouri S&T cDNA Resource Center (www.cdna.org) in cloning vector pcDNA3.1+. The vector containing the human CB2 receptor was transfected directly into CHO-KI cells obtained from ATCC. The HA-tagged human CB1 receptor sequence was subcloned into the pef4-V5-HisA vector with Kpn1 and Pme1 restriction enzymes and subsequently transfected into CHO-K1 cells. Cells were clonally isolated by limited dilution and screened by immunocytochemistry for expression of the HA tag. Clones expressing the HA tag were then screened by RT-PCR to confirm expression of hCB1 and hCB2 receptor mRNA transcripts (data not shown).

Cells were maintained in DMEM/F12 media supplemented with 10% fetal bovine serum (FBS), 100 units/ml penicillin and 100 μg/ml streptomycin and 2 mM L-glutamine. Transfected cell lines were maintained with additional 150ug/ml zeocin for pEF HA-CB1 transfected cells and 500ug/ml G-418 for pcDNA HA-CB2 transfected cells (all reagents obtained from Invitrogen).

MEMBRANE PREPARATION

Cells were grown to confluence and harvested in ice cold phosphate buffered saline with 5 mM EDTA. Cells were spun at 200 x g for 10 min and frozen at -80°C until required. Cell pellets were thawed with cold 0.32 M sucrose and homogenised with a glass homogeniser. The homogenate was spun at 1000 x g for 10 min at 4°C and the supernatant spun in a Sorvall ultracentrifuge for 30 min at 100,000 x g. The pellet was then washed in ice cold water and re-spun twice more. The final pellet was resuspended in 50 mM Tris pH 7.5, 0.5 mM EDTA. Protein concentration was determined using the Dc protein assay kit (BioRad, Hercules, CA, USA).

MEMBRANE COMPETITION BINDING ASSAY

The K_d of CP 55,940 in the isolated CB1 and CB2 receptor expressing membranes was previously determined to be 2.3 nM and 1.5 nM, respectively (see Pertwee, R.G. *Current Medicinal Chemistry* 6 635-664 (1999)). Competition binding assays at 2.5 nM [^{3}H]-CP 55,940 (PerkinElmer) were carried out to determine the K_i values for tested compounds. Membranes (5-10 μg) were incubated with radioligand

and a range of concentrations of test compounds in binding buffer (50 mM Tris pH 7.4, 5 mM $MgCl_2$, 1 mM EDTA) with 0.5% (w/v) bovine serum albumin (BSA) (ICP Bio, New Zealand), at 30°C for 60 min. Stock solutions of putative cannabinoid ligands were prepared in dimethyl sulfoxide to a concentration of 10 mM. Six different final concentrations of compounds were used ranging from 50 µM to 0.1 nM. Non-specific binding was determined in the presence of 1 µM non-radioactive CP 55,940 (Tocris Cookson). Assays were terminated by addition of 2 ml ice cold binding buffer and filtration through GF/C filters (Whatman) pre-soaked in cold binding buffer, followed by two washes in the same buffer.

Radioactivity was determined by incubation of filters with Irgasafe scintillation fluid (PerkinElmer) and scintillation counting in a Wallac Trilux using Microbeta Trilux software. Data was analysed using the Prism 4.02 programme (GraphPad Software, San Deigo, CA, USA).

cAMP Assays

Cells were seeded at a density of 10,000 cells per well in poly-L-lysine treated 96-well culture plates (BD Biosciences). The following day wells were incubated with 40 µl DMEM/F12 containing 0.5% (w/v) BSA and 0.5 mM 3-isobutyl-1-methylxanthine (Sigma-Aldrich) for 30 minutes prior to 15 min stimulation with 50 µM forskolin (Tocris Cookson) and varying concentrations of indicated compounds at 37°C, 5% CO_2. Assays were stopped by removal of media and addition of 100% ice cold ethanol. Plates were then frozen for a minimum of two hours before complete evaporation of ethanol. The well contents were then reconstituted in 50 µl cAMP assay buffer (20 mM HEPES pH 7.5 and 5mM EDTA). Half of the reconstituted sample was transferred to round bottom 96-well plates (Greiner Bio-One GmbH) with 50 µl 0.01% w/v PKA (cAMP dependent protein kinase (Sigma-Aldrich) in 1 mM Na citrate pH 6.5 with 2 mM dithiothreitol) and 25 µl [^{3}H]-cAMP (at 22 nM in cAMP assay buffer) (GE Healthcare, Life Sciences). This was allowed to equilibrate for 3-18 hours. Following this a charcoal slurry (5% (w/v) activated charcoal and 0.2% (w/v) BSA in cAMP assay buffer) was added to the samples and the plates centrifuged at 3000 x g, 4°C for 5 min. Radioactive counts within the supernatant were then determined as described for competition binding assays.

Membrane [^{35}S]GTPγS Binding Assay

Human CB2 expressing CHO-K1 membranes (5 μg per incubation mixture) were diluted in 50 mM Tris-HCl (pH 7.5) and 0.5 mM EDTA and added to HU compounds in a pre-mixed incubation cocktail. Final incubation concentrations were 55 mM Tris-HCl (pH 7.4), 1 mM EDTA, 100 mM NaCl, 5 mM $MgCl_2$, 0.5% BSA, 50 μM GDP, 0.2 nM [^{35}S]GTPγS (PerkinElmer) with varied HU compound concentration and 5 μg membrane. Incubations were continued for 60 minutes at 30°C in a shaking water bath. Assays were terminated by addition of 2 ml ice cold wash buffer (50 mM Tris-HCl, pH 7.5 and 5 mM $MgCl_2$) and filtration through pre-soaked GF/C filters (Whatman), followed by two further washes. adioactivity was determined as described for competition binding assays.

Statistical Analysis

Data was analyzed using the Prism 4.02 programme (GraphPad Software, San Deigo, CA, USA). IC50 and EC50 values, as determined from sigmoidal curves, were generated from drug concentrations plotted in log scale. While the standard error of the mean (SEM) or standard deviation of these values may be calculated while they are in log form the conversion into molar (linear) values becomes uneven and the error is not able to be expressed as "plus or minus" the calculated values. It is possible to display data as an average, plus or minus the standard error of the mean in log form, however, this is not easily interpreted or compared to other values. It was therefore elected to calculate the 95% confidence interval for the mean value in log form and then convert the lower limit, mean and upper limit into the molar (linear) scale. Although the range depicted in this data format often spans a wide range of concentrations, it is a much more user friendly method of displaying data, the data generated in this chapter is comparable to other similar published results of reputable sources (Pertwee *et al.*, 2000). Two-tailed t-tests for statistical analysis between enantiomeric pairs of compounds were performed for CB2 K_i values. The Pearson value, an indication of linearity, was determined for K_i and IC50 or EC50 results obtained for CB2 receptors in binding, cAMP or GTPγS experiments, respectively. To determine if Emax values were significantly different from HU-308, one-way ANOVA was performed with a Bonferroni post-test of selected pairs.

Results

Efficacy and Affinity of Binding to CB1 and CB2 Receptors.

All data was analyzed using Prism 4.02. For binding data the K_i was determined from IC_{50} values derived from competition binding data fitted with one site competition non-linear regression analysis by Prism 4.02 using the K_d values reported above.

pIC_{50} values were determined from cAMP assays by fitting a sigmoidal concentration response curve using Prism 4.02.

Results shown in Tables 1 and 2 were generated by averaging two independently determined pIC_{50} values. Data shown is IC_{50} (95% confidence interval). E_{max} values were calculated as a percentage of the maximal response detected in parallel cAMP assays with HU-210 (1,1-Dimethylheptyl- 11-hydroxy- tetrahydrocannabinol or (6aR)-trans-3-(1,1-Dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methan ol) or HU-308 ([(1R,2R,5R)-2-[2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl]-7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl] methanol) for CB1 and CB2 expressing cells respectively. Data are displayed as the mean ± SEM.

Table 1: Efficacy and affinity of compounds of the invention for the human CB1 and CB2 receptor

		Competition Binding Assay				cAMP Assay					
		CB2 Receptor		CB1 Receptor		CB2 Receptor			CB1 Receptor		
Compound	HU-number	K_i (nM)	95% Confidence Interval	K_i (μM)	95% Confidence Interval	IC_{50} (nM)	95% Confidence Interval	E_{max}	IC_{50} (μM)	95% Confidence Interval	E_{max}
12a	HU-907	2514	(829, 7630)	NB	-	NB	-	-	NB	-	-
12b	HU-908	NB	-	NB	-	NB	-	-	NB	-	-
14a	HU-909	56.8	(24.4, 132)	11.7	(4.90, 27.9)	425	(233, 774)	95±6%	NB	-	-
14b	HU-910	6	(5.25, 6)	1.37	(0.53, 3.56)	162	(87.9, 300)	105±12%	NB	-	-
11a	HU-911	84.6§	(34.9, 204)	NB	-	385	(200, 751)	86±9%	NB	-	-
11b	HU-912	77.1§	(30.0, 199)	>10μM	-	239	(159, 358)	107±4%	3.37	(2.79, 4.06)	112±8%
16a	HU-913	81.5	(69.6, 95.6)	NB	-	330	(195, 557)	101±11%	NB	-	-
16b	HU-914	1500	(870, 2570)	NB	-	2290	(1710, 3050)	82±7%	NB	-	-
20a	HU-917	NB	-	NB	-	NB	-	-	NB	-	-
20b	HU-918	NB	-	NB	-	NB	-	-	NB	-	-
23	HU-926	106	(55.3, 204)	NB	-	321	(203, 511)	100±13%	NB	-	-
25	HU-928	230	(36.7, 1450)	NB	-	925	(550, 1560)	101±11%	NB	-	-
22	HU-936	1720	(827, 3560)	NB	-	NB	-	-	NB	-	-
24	HU-938	7910	(4610, 13600)	NB	-	NB	-	-	NB	-	-
15a	HU-969	6460	(4800, 7890)	NB	-	NB	-	-	NB	-	-
15b	HU-970	1270	(634, 2530)	NB	-	1150	(664, 1980)	38±2%*	NB	-	-
13a	HU-971	704	(314, 1580)	NB	-	1530	(810, 2900)	31±4%*	NB	-	-
13b	HU-972	168	(115, 247)	NB	-	313	(220, 446)	48±5%*	NB	-	-
17a	HU-973	1150	(596, 2210)	NB	-	2090	(1340, 3260)	40±6%*	NB	-	-
17b	HU-974	>10μM	-	NB	-	NB	-	-	NB	-	-
	HU-308	14	(8.7, 22.8)	NB	-	117	(89.5, 153)	100±0%	NB	-	-
	HU-210			0.00294							

Competition binding assays were performed with either CHO-CB1 or CHO-CB2 cellular membranes and cAMP assays in whole cells expressing the indicated receptor. Binding (K_i) and potency (EC50) data is presented as the mean with 95 % confidence intervals in parentheses. cAMP derived efficacy data (Emax) is presented as the mean ± SEM. All data was calculated from at least three independent repeats. * $P<0.01$ compared to HU-308 Emax. § Enantiomer pair with a lack of statistical significance. NB = No binding or activity detected at concentrations up to 50 μM. >10 μM = Displacement of radioactive ligand detected at high concentrations competing ligand but complete displacement curves were not obtained.

EFFICACY OF BINDING TO CB2 RECEPTORS.

This assay was performed for selected high potency compounds. EC_{50} values were determined from [^{35}S]GTPγS assays by fitting a sigmoidal concentration response curve (Table 2 and Figure **1A-1G**). E_{max} values were calculated as a percentage of the maximal response detected in parallel [^{35}S]GTPγS assays with HU-308. As the E_{max} values are determined on a linear scale (not a log of %) these are displayed as the mean ± SEM. A Pearson value of 0.9268, indicating good correlation between the data, was generated by plotting the K_i values of compounds against their EC_{50}'s determined by GTPγS assay.

Table 2: Efficacy of compounds of the invention for the human CB2 receptor

Compound	HU-Number	EC_{50} (nM)	E_{max}
14a	HU-909	135.5 (45.4, 404)	76±7%*
14b	HU-910	26.4 (10.7, 65.5)	121±7%
11a	HU-911	126.2 (50.7, 315)	94±4%
16a	HU-913	343.6 (151, 785)	98±3%
23	HU-926	184.9 (72.1, 474)	51±6%**
25	HU-928	576.8 (291, 1140)	95±5%
	HU-308	18.3 (11.6, 28.8)	100±0%

Data is shown as mean EC50 values with 95% confidence interval values in parentheses. Mean E_{max} values (± SEM) have been normalised to HU-308 E_{max} response. n=5 *P<0.05, **P<0.001.

Figs. 1A-1G show the GTPγS binding graphs for human CB2 receptor of compounds of the invention: HU-308 (Fig. 1A), HU-909 (Fig. 1B), HU-910 (Fig. 1C), HU-911 (Fig. 1D), HU-913 (Fig. 1E), HU-926 (Fig. 1F) and HU-928 (Fig. 1G). Data is shown as [^{35}S]GTPγS binding normalised to maximal HU-308 binding under the same experimental conditions.

EXAMPLE 3: *IN VIVO* EFFECT OF HU-910 ON CLOSED HEAD INJURY

CLOSED HEAD INJURY MODEL AND NEUROBEHAVIORAL EVALUATION

The study was conducted according to the guidelines of the Institutional Animal Care Committee of the Hebrew University. Male Sabra mice weighing 35 to 50 g were used in all experiments. Animals were kept under controlled light conditions with a 12 h/12 h light/dark cycle. Experimental closed head injury (CHI) was induced using a modified weight drop device developed in our laboratory as described previously (Chen et al., 1996). At 1 h after CHI, the functional status of the mice was evaluated according to a set of 10 neurobehavioral tasks, namely the neurological severity score (NSS). This score is based on the ability of the mice to perform 10 different tasks (Beni-Adani et al., 2001) that evaluate their motor ability, balance, and alertness. One point is given for failing to perform a task. The severity of injury is indicated by the initial NSS, which is evaluated 1 h after CHI and is also a reliable predictor of the later outcome. A score of 10 reflects maximal neurologic impairment, and a decrease of NSS during the recovery period indicates partial recovery of function.

STATISTICAL ANALYSIS

Data was analyzed using the Prism 4.02 programme (GraphPad Software, San Deigo, CA, USA). The data are expressed as mean ± SEM and statistical significance was assessed with one way analysis of variance (ANOVA) followed by a Dunnett's post-hoc analysis for TNF-α levels. Nonparametric NSS values were compared between the two groups at each time point. These data were analyzed for differences between groups at individual times (and not over time within the same group). Hence, Mann–Whitney tests were used for comparisons.

***IN VIVO* EXPERIMENT 1:**

In this study four groups of mice were subjected to CHI (n=10/group and control n=9), after which the following agents were administered:

- *Group 1 (Control)*: Vehicle only (ethanol:cremophor:saline at ratio of 1:1:18), 1h after CHI.
- *Group 2:* HU-910, 0.1mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.
- *Group 3:* HU-910, 1.0mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.

- *Group 4:* HU-910, 10.0mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.

The Neurological Severity Score (NSS) was followed during 21 days, and the extent of recovery (measured as ΔNSS= NSS(1h)–NSS(t)) was calculated and presented in **Fig. 2**. It is noted that the most effective dose of **HU-910** was 10 mg/kg. At days 5 and 7 post injury, the treated mice displayed a significant greater recovery than the controls (vehicle-treated) or lower doses (**HU-910** at 0.1 and 1 mg/kg) treated groups.

***IN VIVO* EXPERIMENT 2:**

In this study four groups of mice were subjected to CHI (n=9/group), after which the following agents were administered:

- *Group 1(Control)*: Vehicle only (ethanol:cremophor:saline at ratio of 1:1:18), 1h after CHI.
- *Group 2:* HU-910, 10mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.
- *Group 3:* Specific CB2 antagonist SR144528 (*N*-[(1*S*)-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)pyrazole-3 carboxamide), (see M. Rinaldi-Carmona, et al. *J. Pharmacol. Exp. Ther.* 284 (1998) 644–650), 1mg/kg, i.p. 1h after CHI.
- *Group 4:* Specific CB2 antagonist (SR144528, *N*-[(1*S*)-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)pyrazole-3 carboxamide), 1mg/kg, i.p. 1h after CHI and HU-910 10mg/kg administered 10 min after administration of antagonist.

It is noted that groups 3 and 4 were administered in order to verify that HU-910 indeed acts via the CB2 receptor.

Fig. 3 depicts the extent of recovery of the four groups (measured as ΔNSS= NSS(1h)–NSS(t)), for a period of 24h to 14day post CHI), from which it can be appreciated that in the presence of the antagonist alone (Group 3), the recovery was significantly reduced as compared with the control group (Group 1), administered with the vehicle alone. Moreover, the beneficial effect of **HU-910** was reduced to a similar extent in the presence of the antagonist (Group 4). These findings suggest that **HU-910** exerts its effect via the CB2 receptor. Thus, it is also stipulated that the endogenous

ligands, 2-AG and anandamide that exert their neuro-protective effect by stimulating of the CB2 receptors, provide protection at the post-CHI period, such that when the CB2 receptor is blocked (e.g. with antagonist), their effect is eliminated as well, leading to retarded recovery.

***IN VIVO* EXPERIMENT 3:**

In this study four groups of mice were subjected to CHI (n=7-8/group), after which the following agents were administered:

- *Group 1(Control)*: Vehicle only (Dimethyl Sulfoxide (DMSO): Tween 80: Saline at ratio of 1:1:18), i.p. 1h after CHI.
- *Group 2:* HU-910, 10mg/kg, dissolved in Vehicle, i.p. 1h after CHI.
- *Group 3:* Specific CB2 antagonist/ inverse agonist AM630 (6-Iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl](4-methoxyphenyl)methanone) (Ross et al. 1999)), dissolved in Vehicle, 1mg/kg, i.p. 1h after CHI and HU-910, dissolved in Vehicle, 10mg/kg administered 10 min after administration of antagonist/ inverse agonist.
- *Group 4:* Specific CB2 antagonist/ inverse agonist AM630 (6-Iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl](4-methoxyphenyl)methanone), dissolved in Vehicle, 1mg/kg, i.p. 1h after CHI

It is noted that groups 3 and 4 were administered in order to verify that HU-910 indeed acts via the CB2 receptor.

Fig. 4 depicts the recovery of the four groups measured as ΔNSS, for a period of 1h to 28 days post CHI, from which it can be appreciated that the beneficial effect of HU-910 (Group 2) was reduced to a similar extent in the presence of the antagonist/ inverse agonist (Group 3). These findings suggest that HU-910 exerts its effect via the CB2 receptor.

IN VIVO EFFECT OF HU-914 ON CLOSED HEAD INJURY

IN VIVO EXPERIMENT 4:

In this study four groups of mice were subjected to CHI (n=10/group), after which the following agents were administered:

- *Group 1 (Control)*: Vehicle only (ethanol:cremophor:saline at ratio of 1:1:18), 1h after CHI.
- *Group 2:* HU-914, 5mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.
- *Group 3:* HU-914, 10mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.
- *Group 4:* HU-914, 20mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.

The Neurological Severity Score (ΔNSS) was followed during 21 days and presented in **Fig. 5**. The most effective dose of **HU-914** was 5 mg/kg. Starting at 3 days post injury, the treated mice with **HU-914** 5mg/kg displayed a significant greater recovery than the controls (vehicle-treated) or higher doses (**HU-914** 10 mg/kg and 20 mg/kg) treated group.

IN VIVO EXPERIMENT 5:

In this study three groups of mice were subjected to CHI (n=10/group), after which the following agents were administered:

- *Group 1(Control)*: Vehicle only (ethanol:cremophor:saline at ratio of 1:1:18), 1h after CHI.
- *Group 2:* HU-914, 5mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.
- *Group 3:* Specific CB2 antagonist/ inverse agonist (SR144528, *N*-[(1*S*)-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)pyrazole-3 carboxamide), 1mg/kg, i.p. 1h after CHI and HU-914 5mg/kg administered 10 min after administration of antagonist/ inverse agonist.

Fig. 6 depicts the extent of recovery of the four groups (measured as ΔNSS= NSS(1h)–NSS(t), for a period of 24h to 28 day post CHI), from which it can be appreciated that in the presence of the antagonist/ inverse agonist (Group 3), the recovery achieved by **HU-914** (Group 2) was abolished and reduced to a similar extent as in the control group (Group 1), administered with the vehicle alone. These findings suggest that, at least partially, **HU-914** exerts its effect via the CB2 receptor.

***IN VIVO* EXPERIMENT 6:**

In this study four groups of male, C57Bl mice were subjected to CHI (n=7-10/group), after which the following agents were administered:

- *Group 1 (Control)*: Vehicle only (ethanol:cremophor:saline at ratio of 1:1:18), i.p. 1h after CHI.
- *Group 2:* HU-914, 2.5mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.
- *Group 3:* HU-914, 5mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.
- *Group 4:* HU-914, 10mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.

The Neurological Severity Score (NSS) was followed during 14 days and presented in **Fig. 7**. It is noted that the most effective doses of **HU-914** in a particular strain of mice were 2.5 mg/kg and 5 mg/kg. At days 14 post injury, the treated mice with **HU-914** (2.5 mg/kg and 5 mg/kg) displayed a significant greater recovery than the controls (vehicle-treated) or higher dose (**HU-914** at 10 mg/kg) treated group. Similar to Sabra mice, this study represents a dose-response effect of **HU-914** in C57Bl mice, in which the lower doses (HU-914 2.5 and 5 mg/kg) were more effective than a higher dose (HU-914 10 mg/kg) or vehicle.

THE EFFECT OF HU-914 ON TNF-α PRODUCTION FOLLOWING CHI.

TNF-α activity can be induced by ischemic and traumatic brain injury starting at 1-2 h and reaching the peak at 4 h following CHI. (Shohami et al., 1997). The next step was to investigate the effect of HU-914 on TNF-α production after CHI.

Three groups of mice (n=5-6) were subjected to CHI:

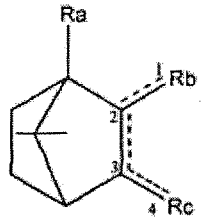
- *Group 1 (Control)*: Sham controls received anesthesia and skin incision only.
- *Group 2:* Vehicle only (ethanol:cremophor:saline at ratio of 1:1:18), i.p. 1h after CHI.
- *Group 3:* HU-914, 5mg/kg, dissolved in vehicle (1:1:18 ethanol:cremophor:saline), i.p. 1h after CHI.

The animals were sacrificed 4 hrs after CHI by decapitation. Brains were rapidly removed and dissected into ipsilateral and contralateral cortical and hippocampal segments that were frozen in liquid nitrogen and kept at -78. The brain tissues were homogenized in ice-cold lysis buffer (50 mM Tris-HCl, 1 mM EDTA, 1 mM EGTA, 0.5 mM Na_3VO_4, 0.1% 2-mercaptoethanol, 1% Triton X-100, 50 mM NaF, 5 mM sodium pyrophosphate, 10 mM sodium β-glyceropyrophosphate, 0.1 mM phenylmethanesulfonyl fluoride, and protease inhibitor mixture) (Roche Diagnostics, Indianapolis, IN). Following sonication on ice for 45 s and centrifugation at 12,000 rpm for 20 min, protein concentrations in the supernatants were determined using the Bradford method (Bio-Rad Laboratories, Munich, Germany). Supernatants were analyzed by enzyme-linked immunosorbent assay (ELISA) for production of TNF-α, using cytokine specific kit from R&D Systems (Minneapolis, MN). HU-914 inhibited TNF-α production in the hippocampus of the injured, left hemisphere, but did not affect the cytokine's level in the left cortex. TNF-α elevation was not detected in the right cortex or hippocampus (**Fig. 8**).

CLAIMS:

1. A method for stimulating a CB receptor in a subject in need thereof, said method comprising administering to said subject a therapeutically effective amount of a compound according to

a compound of general formula (I)



(I)

wherein

1 ------ 2, 2 ------ 3, 3 ------ 4

are each independently a single or double bond;

R_a is selected from an straight or branched Ci-C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C2-C5 alkynyl and -C(=0)Rd, each optionally substituted by at least one group selected from -OH, -COOH, -NH_2, C Cs amine, halogen, phenyl, heteroaryl; wherein

Rd is selected from the group consisting of -H, -OH, straight or branched $C_\backslash$- C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl, straight or branched C C_5 alkoxy, -NReRf;

Re and Rf are each independently selected from H and straight or branched C]-C_5 alkyl; and

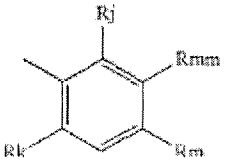
Rb and Rc are each independently selected from -H, -OH, =0, =CR_gRh, =NRj, =S, -C_5-C_{15} aryl ring substituted by at least one group selected from a straight or branched Cj-C^ alkyl, C_2-Ci_2 alkenyl, C_2-C_{12} alkynyl, CrC_{12} alkoxy, amine, CrC_{12} alkoxycarboxylic acid, -OH, -$OC(=0)R_p$ and -C(=0)Rq; wherein

R_g, Rh, Ri, R_p and Rq are each independently selected from H, straight or branched d-C_5 alkyl, straight or branched C1-C5 alkoxy and -NH_2; and provided that at least one of Rb and

Rc is said substituted -C_5-Ci_5 aryl ring;

wherein at least one of R_b and R_c is a group of formula (II'):

(II')



wherein R_j and R_k are each independently selected from H, and —OR_n, wherein R_n is selected from H, a straight or branched C_1-C_5 alkyl, provided that at least one of R_j and R_k is different than H; R_m is selected from a straight or branched C_3-C_{12} alkyl, and R_{mm} is H.

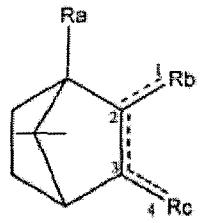
2. A method according to claim 1, wherein said CB receptor is a CB2 receptor.

3. A method according to claims 1 or 2, wherein said stimulation is associated with the treatment of at least one disease, disorder or condition.

4. A method according to claim 3 , wherein said at least one disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof.

5. A process for the preparation of a compound of general formula (I), according to

a compound of general formula (I)



(I)

wherein

1=====2, 2=====3, 3=====4,

are each independently a single or double bond;

R_a is selected from an straight or branched Ci-C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C2-C5 alkynyl and -C(=0)Rd, each optionally substituted by at least one group selected from -OH, -COOH, -NH_2, C Cs amine, halogen, phenyl, heteroaryl; wherein

Rd is selected from the group consisting of -H, -OH, straight or branched C\- C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl, straight or branched C C_5 alkoxy, -NReRf;

Re and Rf are each independently selected from H and straight or branched C]-C_5 alkyl; and

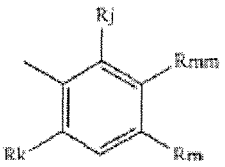
Rb and Rc are each independently selected from -H, -OH, =0, =CR_gRh, =NRj, =S, -C_5-C_{15} aryl ring substituted by at least one group selected from a straight or branched Cj-C^ alkyl,

C_2-Ci_2 alkenyl, C_2-C_{12} alkynyl, CrC_{12} alkoxy, amine, CrC_{12} alkoxycarboxylic acid, -OH, -$OC(=0)R_p$ and -$C(=0)Rq$; wherein

R_g, Rh, Ri, R_p and Rq are each independently selected from H, straight or branched d-C_5 alkyl, straight or branched C1-C5 alkoxy and -NH_2; and provided that at least one of Rb and Rc is said substituted -C_5-Ci_5 aryl ring;

wherein at least one of R_b and R_c is a group of formula (II'):

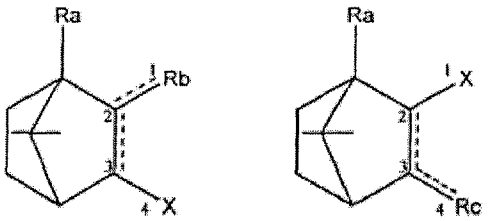
(II')



wherein R_j and R_k are each independently selected from H, and —OR_n, wherein R_n is selected from H, a straight or branched C_1-C_5 alkyl, provided that at least one of R_j and R_k is different than H; R_m is selected from a straight or branched C_3-C_{12} alkyl, and R_{mm} is H,

said process comprising:

(a) providing a compound having the general formula (X) or (X'):



(X) (X')

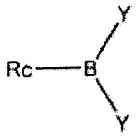
wherein R_a, ¾ and R_c have the same meaning as defined herein above; X is a halide, pseudohalide, functional leaving group; and

1=====2, 2=====3,

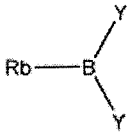
3=====4

are each independently a single or double bond;

(b) reacting compound (X) or (X') with a compound having the general formula (XI) or (XI') respectively:



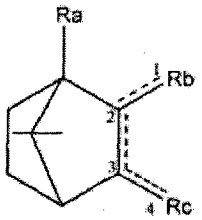
(XI')



(XI)

wherein each of Y is selected from OH, Q-Q alkoxy or both may form a cyclic dialkoxy ring together with the boron atom they are attached to, in the presence of a catalyst; thereby obtaining a compound of formula (I):

6. A process for the preparation of a compound of general formula (I), according to a compound of general formula (I)



(I)

wherein

1 ═══ 2, 2 ═══ 3, 3 ═══ 4;

are each independently a single or double bond;

R_a is selected from an straight or branched Ci-C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C2-C5 alkynyl and -C(=0)Rd, each optionally substituted by at least one group selected from -OH, -COOH, -NH_2, C Cs amine, halogen, phenyl, heteroaryl; wherein

Rd is selected from the group consisting of -H, -OH, straight or branched C\- C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl, straight or branched C C_5 alkoxy, -NReRf;

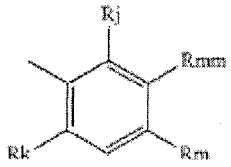
Re and Rf are each independently selected from H and straight or branched C]-C_5 alkyl; and

Rb and Rc are each independently selected from -H, -OH, =0, =CR_gRh, =NRj, =S, -C_5-C_{15} aryl ring substituted by at least one group selected from a straight or branched Cj-C^ alkyl, C_2-Ci_2 alkenyl, C_2-C_{12} alkynyl, CrC_{12} alkoxy, amine, CrC_{12} alkoxycarboxylic acid, -OH, -OC(=0)R_p and -C(=0)Rq; wherein

R_g, Rh, Ri, R_p and Rq are each independently selected from H, straight or branched d-C_5 alkyl, straight or branched C1-C5 alkoxy and -NH_2; and provided that at least one of Rb and Rc is said substituted -C_5-Ci_5 aryl ring;

wherein at least one of R_b and R_c is a group of formula (II'):

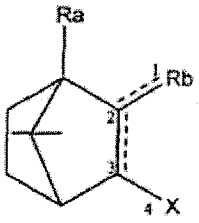
(II')



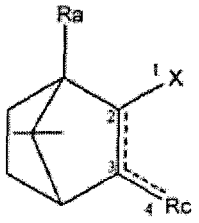
wherein R_j and R_k are each independently selected from H, and —OR_n, wherein R_n is selected from H, a straight or branched C_1-C_5 alkyl, provided that at least one of R_j and R_k is different than H; R_m is selected from a straight or branched C_3-C_{12} alkyl, and R_{mm} is H,

said process comprising:

(a) providing a compound having the general formula (X) or (X'):



(X)



(X')

wherein R_a, R_b and R_c have the same meaning as defined herein above; X is a halide, pseudohalide, functional leaving group; and

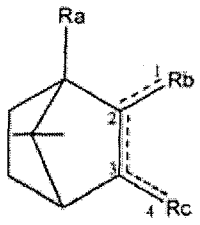
1=====2, 2=====3,

3=====4

are each independently a single or double bond;

(b) coupling compound (X) or (X') with R_c-H or R_b-H respectively; thereby obtaining a compound of formula (I).

7. A compound of general formula (I):



(I)

wherein

1 ------ 2, 2 ------ 3, 3 ------ 4 are each independently a single or double bond;

R_a is selected from an straight or branched C -Cs alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl and -C(=0)Rd, each optionally substituted by at least one group selected from -OH, -COOH, -NH_2, CrC_5 amine, halogen, phenyl, heteroaryl; wherein

Rd is selected from the group consisting of -H, -OH, straight or branched C\- C_5 alkyl, straight or branched C_2-C_5 alkenyl, straight or branched C_2-C_5 alkynyl, straight or branched Cj- alkoxy, -NReRf;

Re and Rf are each independently selected from H and straight or branched C!-C_5 alkyl; and

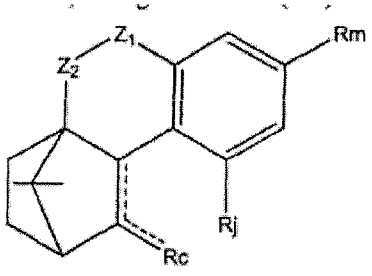
¾ and Rc are each independently selected from -H, -OH, =0, =CR_gRh, =NRj, =S, -C_5-C_{15} aryl ring substituted by at least one group selected from a straight or branched CrC_{12} alkyl, C_2-Cj_2 alkenyl, C_2-C_{12} alkynyl, Q-C_{12} alkoxy, amine, C]-C_{12} alkoxycarboxylic acid, -OH, -OC(=0)R_p and -C(=0)Rq; wherein

R_g, Rh, Rj, R_p and Rq are each independently selected from H, straight or branched C1-C5 alkyl, straight or branched C1-C5 alkoxy and -NH_2;

or R_a and R may form a ring together with the carbon atoms they are each attached to; said ring may be a cycloalkyl, cycloheteroalkyl, cycloheteroalkenyl, cycloalkenyl, cycloalkynyl, cycloheteroalkynyl ring;

provided that at least one of Rb and Rc is said substituted -C5-C_{15} aryl ring.

8. A compound of claim 7, having the formula (XII):



(XII)

wherein ------
is a single or double bond;

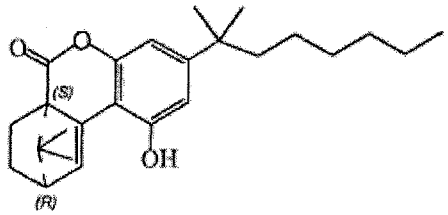
Rc is selected from -H, -OH, =0, =CR_gR_h, =NRj, =S, -C_5-Ci_5 aryl ring substituted by at least one group selected from a straight or branched Ci-Ci_2 alkyl, C_2-C_{12} alkenyl, C_2-Ci_2 alkynyl, Ci-C_{12} alkoxy, amine, C\-C\2 alkoxycarboxylic acid, - OC(=0)R_p and -C(=0)$R_{<1}$; wherein R_g, ¾, Ri, R_p and Rq are each independently selected from H, straight or branched Cj-Cs alkyl, straight or branched C_t-Cs alkoxy and -NH_2;

Rj is selected from H, and -OR_n wherein R_n is selected form H, -$COOR_t$, a straight or branched Ci-C_5 alkyl optionally substituted by at least one group selected from -COOH, -NH_2; and R, is selected from H, Q-Cs alkyl and -NH_2;

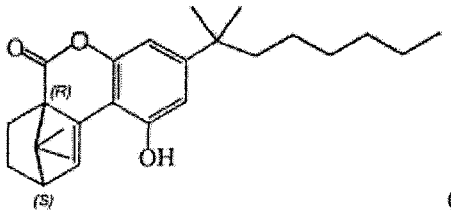
Rm is selected from a straight or branched C_6-C_{12} alkyl, a straight or branched C_5-C_9 alkoxy, a straight or branched C C_7 ether; each optionally substituted by at least one group selected from -COOH, -NH_2;

$Z_\backslash$ and Z_2 are each independently selected from -0-, straight or branched C1-C5-alkylene, -S-, -C(=0)- and -C(=S)-.

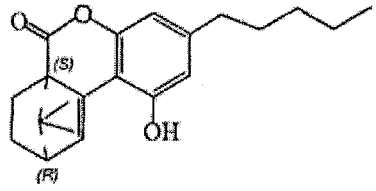
9. The compounds according to claims 7 or 8, being selected from the group consisting of:



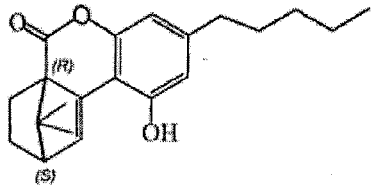
(26),



(27),



(28),



(29).

10. A compound according to claims 7 to 9, capable of stimulating a CB receptor.

11. A compound according to claim 10, wherein said receptor is a CB2 receptor.

12. A compound according to claims 10 or 11, wherein said stimulation is associated with the treatment of a disease, disorder or condition.

13. A compound according to claim 12, wherein said disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-

fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof.

14. A compound according to claim 13 wherein said disease, disorder or condition is cerebral injury.

15. A compound according to claim 14, wherein said cerebral injury is selected from closed head injury, penetrating head injury, blast injury, cerebral ischemic-reperfusion injury, post-operable brain injury, brain hemorrhaging.

16. A compound according to any one of claims 7 to 9, capable of lowering secondary damage produced by brain trauma.

17. A compound according to any one of claims 7 to 9 for use as a medicament.

18. A compound according to any one of claims 7 to 9 for use in the treatment of disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof.

19. A compound according to claims 7 to 9, for use in the treatment of cerebral injury.

20. A compound according to claim 19, wherein said cerebral injury is selected from close head injury, open head injury, cerebral ischemic-reperfusion injury, post-operable brain injury, brain hemorrhaging.

21. A compound according to any one of claims 7 to 9, for use in lowering secondary damage produced by brain trauma.

22. A compound according to any one of claims 7 to 9, for use in the stimulation of bone growth, bone mass, bone repair or prevention of bone loss.

23. A compound according to claim 22, for use in the treatment of at least one disease or a disorder selected from osteopenia, osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, osteoarthritis, periodontal disease or defect, an osteolytic bone loss disease, post-plastic surgery, post-orthopedic surgery, post oral surgery, post-orthopedic implantation, and post-dental implantation, primary and metastatic bone cancer, osteomyelitis, or any combinations thereof.

24. A compound according to claim 23, wherein said at least one disease or disorder is selected from osteopenia and osteoporosis.

25. A pharmaceutical composition comprising a compound according to any one of claims 7 to 9.

26. A pharmaceutical composition according to claim 25, for use in the treatment of disease, disorder or condition is selected from inflammation, pain, allergies, neurological and

neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof.

27. A pharmaceutical composition according to claim 26, wherein said disease, disorder or condition is cerebral injury.

28. A pharmaceutical composition according to claim 27, wherein said cerebral injury is selected from close head injury, open head injury, cerebral ischemic-reperfusion injury, post-operable brain injury, brain hemorrhaging.

29. A pharmaceutical composition according to claim 25, for use in lowering secondary damage produced by brain trauma.

30. A pharmaceutical composition according to claim 25, for use in the stimulation of bone growth, bone mass, bone repair or prevention of bone loss.

31. A pharmaceutical composition according to claim 30, for use in the treatment of at least one disease or a disorder selected from osteopenia, osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, osteoarthritis, periodontal disease or defect, an osteolytic bone loss disease, post-plastic surgery, post-orthopedic surgery, post oral surgery, post-orthopedic implantation, and post-dental implantation, primary and metastatic bone cancer, osteomyelitis, or any combinations thereof.

32. A pharmaceutical composition according to claim 31, wherein said at least one disease or disorder is selected from osteopenia and osteoporosis.

33. Use of a compound of claims 7 to 9, for the manufacture of a pharmaceutical composition.

34. Use of a compound according to claims 7 to 9, for the manufacture of a medicament capable of stimulating a CB receptor.

35. Use of a compound according to claim 34, wherein said receptor is a CB2 receptor.

36. Use of a compound according to claims 34 or 35, wherein said stimulation is associated with the treatment of at least one disease, disorder or condition.

37. Use of a compound according to claim 36, wherein said at least one disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof.

38. Use of a compound according to claims 7 to 9, for the manufacture of a medicament for the treatment of cerebral injury.

39. Use of a compound according to claim 38, wherein said cerebral injury is selected from closed head injury, penetrating head injury, blast injury, cerebral ischemic-reperfusion injury, post-operable brain injury, brain hemorrhaging.

40. Use of a compound according to any one of claims 7 to 9, for the manufacture of a medicament for lowering secondary damage produced by brain trauma.

41. Use of a compound according to any one of claims 7 to 9, for the preparation of a pharmaceutical composition for stimulation of bone growth, bone mass, bone repair or prevention of bone loss.

42. Use of a compound according to claim 41, wherein said stimulation of bone growth, bone mass, bone repair or prevention of bone loss are associated with the treatment of at least one disease or a disorder selected from osteopenia, osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, osteoarthritis, periodontal disease or defect, an osteolytic bone loss disease, post-plastic surgery, post-orthopedic surgery, post oral surgery, post-orthopedic implantation, and post-dental implantation, primary and metastatic bone cancer, osteomyelitis, or any combinations thereof.

43. Use of a compound according to claim 42, wherein said at least one disease or disorder is selected from osteopenia and osteoporosis.

44. A method for stimulating a CB receptor in a subject in need thereof, said method comprising administering to said subject a therapeutically effective amount of a compound according to any one of claims 7 to 9.

45. A method according to claim 44, wherein said CB receptor is a CB2 receptor.

46. A method according to claims 44 or 45, wherein said stimulation is associated with the treatment of at least one disease, disorder or condition.

47. A method according to claim 46, wherein said at least one disease, disorder or condition is selected from inflammation, pain, allergies, neurological and neurodegenerative diseases, liver diseases, cerebral injury, cancer, retinal vascularization, endometritis, appetite related disorders, metabolic syndrome, diabetes, atherosclerosis; disorders related to anti-fibrinogenic effects, inflammatory bowel disease, arthritis and emesis, or any combination thereof.