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(54) Title: NOVEL HETEROPYRROLE ANALOGS ACTING ON CANNABINOID RECEPTORS

(57) Abstract: Disclosed are biologically active hetero pyrrole analogs such as imidazoles, thiazoles, oxazoles and pyrazoles capable of interacting with the CB1 and/or the CB2 cannabinoid receptors. One aspect discloses hetero pyrrole analogs acting as antagonists for the CB1 and/or the CB2 receptors. Another aspect discloses hetero pyrrole analogs having selectivity for the CB1 or CB2 cannabinoid receptor. Also disclosed are pharmaceutical preparations employing the disclosed analogs and methods of administering therapeutically effective amounts of the disclosed analogs to provide a physiological effect.



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NOVEL HETEROPYRROLE ANALOGS ACTING ON CANNABINOID RECEPTORS

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5 This invention was made with Government support under Grant No. DA7215 awarded by the National Institute on Drug Abuse. The Government may have certain rights in the invention.

Field of the Invention

10 The present invention relates generally to biologically active hetero pyrrole analogs such as imidazoles, thiazoles, oxazoles and pyrazoles capable of interacting with the CB1 and/or the CB2 cannabinoid receptors. One aspect of the invention is concerned with new and improved hetero pyrrole analogs acting as antagonists for the CB1 and/or the CB2 receptors. Another aspect of the
15 invention is concerned with new and improved hetero pyrrole analogs having selectivity for the CB1 or CB2 cannabinoid receptor. Still other aspects of the invention are concerned with pharmaceutical preparations employing the inventive analogs and methods of administering therapeutically effective amounts of the inventive analogs to provide a physiological effect.

20

Background of the Invention

Marijuana (*Cannabis sativa*) and derivatives have been used for medicinal and recreational purposes. The major active constituent extracted from *Cannabis sativa* is the classical cannabinoid Δ^9 -Tetrahydrocannabinol (Δ^9 -THC). The effects
25 of such cannabinoids are due to an interaction with specific high-affinity receptors. Presently, two cannabinoid receptors have been characterized: CB1, a central receptor found in the mammalian brain and a number of other sites in peripheral tissues; and CB2, a peripheral receptor found principally in cells related to the immune system. The CB1 receptor is believed to mediate the psychoactive
30 properties associated with classical cannabinoids. Characterization of these receptors has been made possible by the development of specific synthetic ligands such as the agonists WIN 55212-2 and CP 55,940.

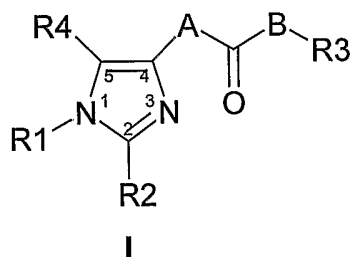
In addition to acting at the cannabinoid receptors, cannabinoids such as Δ^9 -THC also affect cellular membranes, thereby producing undesirable side effects

such as drowsiness, impairment of monoamine oxidase function and impairment of non-receptor mediated brain function. The addictive and psychotropic properties of some cannabinoids also limit their therapeutic value.

International Publication number WO 03/007887 A2 to Finke et al describes imidazole derivatives alleged to have binding affinity for the central cannabinoid receptor. International Publication number WO 03/027076 A2 to Kruse et al also describes some imidazole derivatives alleged to have binding affinity for cannabinoid receptors.

10 Summary of the Invention

Briefly stated, one embodiment of the invention is concerned with new and improved cannabimimetic (cannabinoid like) imidazole analogs. The inventive cannabimimetic imidazole ligands of this embodiment can be represented by general formula I:



A comprises a direct bond, O or $-(CH_2)_lN(R_5)$.

B comprises a direct bond, O or $N(R_5)$.

20 R_5 is hydrogen, alkyl or substituted alkyl and l is 0 or 1.

In a variation of formula I R_1 and R_2 each independently comprise $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

25 Z comprises H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

5 X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

j is an integer from 0 to about 6.

10 In a variation of formula I R_1 and R_2 each independently comprise $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7
15 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted
20 benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

25 In a variation of formula I R_1 and R_2 each independently comprise $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

Z comprises a 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a substituted 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a 6 member
30 aromatic ring having 0 to 5 independently selected heteroatoms as ring members or a substituted 6 member aromatic ring having 0 to 5 independently selected heteroatoms; and wherein the connecting point between the $-(CH_2)_n-$ group and

the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of formula I R1 and R2 each independently comprise
5 $-(CH_2)_n-Z$.

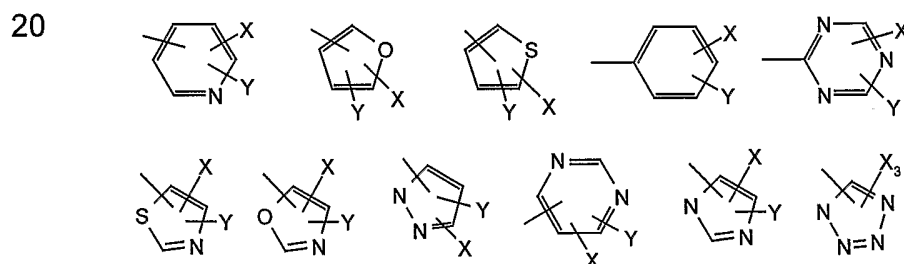
n is an integer from 0 to about 7.

Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl,
10 ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any
15 available ring nitrogen atom.

In a variation of formula I, R1 and R2 each independently comprise $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

Z comprises



wherein X and Y each independently comprise H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure
30 having two adjacent carbon atoms.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

5 X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

In a variation of formula I R_1 and R_2 each independently $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

10 Z comprises a carbocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a carbocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an heterocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5
15 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heteroaromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms or a heteroaromatic ring having 6 ring atoms fused to a heteroaromatic ring having
20 from 5 to 7 ring atoms.

In a variation of formula I R_1 and R_2 each independently comprise $-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

25 Z comprises an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7
30 ring atoms and 0 to 3 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 4 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members.

In a variation of formula I R1 and R2 each independently comprise
 $-(CH_2)_m-Q_1-(CH_2)_n-Z$.

Q_1 comprises N, O, S, $-CH=CH-$, $-C\equiv C-$, $-CO$, SO_2 or OSO_2 .

5 m is an integer from 1 to about 7

n is an integer from 0 to about 7.

Z comprises H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-
 aroyl, $O(CH_2)_jOH$, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aroyl, CHO,
 C(halogen)₃, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alkoxy, alkylmercapto,
 10 alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about
 4 to about 7 ring members and optionally one additional heteroatom
 selected from O, N or S, or

15 X_1 and X_2 together comprise part of an imide ring having about 5 to
 about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

j is an integer from 0 to about 6.

20 In a variation of formula I R1 and R2 each independently comprise
 $-Q_2-(CH_2)_n-Z$.

Q_2 is optionally present and if present comprises $-CH_2-N$, $-CH_2-O$, $-CH_2-S$,
 $-CH_2-SO_2$ or $-CH_2-OSO_2$.

n is an integer from 0 to about 7.

25 Z comprises H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-
 aroyl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aroyl, CHO, C(halogen)₃, $COOX_3$,
 SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino,
 alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

30 X_1 and X_2 together comprise part of a heterocyclic ring having about
 4 to about 7 ring members and optionally one additional heteroatom
 selected from O, N or S, or

X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members.

X₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX₁X₂.

j is an integer from 0 to about 6.

5

In a variation of formula I R₁ and R₂ each independently comprise

-(CH₂)_m-Q₁-(CH₂)_n-Z.

Q₁ comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

m is an integer from 1 to about 7

10

n is an integer from 0 to about 7.

Z comprises a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

In a variation of formula I R₁ and R₂ each independently comprise

15

-(CH₂)_m-Q₁-(CH₂)_n-Z.

Q₁ comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

m is an integer from 1 to about 7.

n is an integer from 0 to about 7.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a
 20 heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members; a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring or any above group substituted on at least one available ring atom by an alkyl group or any above group substituted on
 25 at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the -(CH₂)_n- group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

30

In a variation of formula I R₁ and R₂ each independently comprise

-(CH₂)_m-Q₁-(CH₂)_n-Z.

Q₁ comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

m is an integer from 1 to about 7.

n is an integer from 0 to about 7.

Z comprises a 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a substituted 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a 6 member aromatic ring having 0 to 5 independently selected heteroatoms as ring members or a substituted 6 member aromatic ring having 0 to 5 independently selected heteroatoms; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of formula I R1 and R2 each independently comprise $-(CH_2)_m-Q_1-(CH_2)_n-Z$.

Q_1 comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

m is an integer from 1 to about 7.

n is an integer from 0 to about 7.

Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

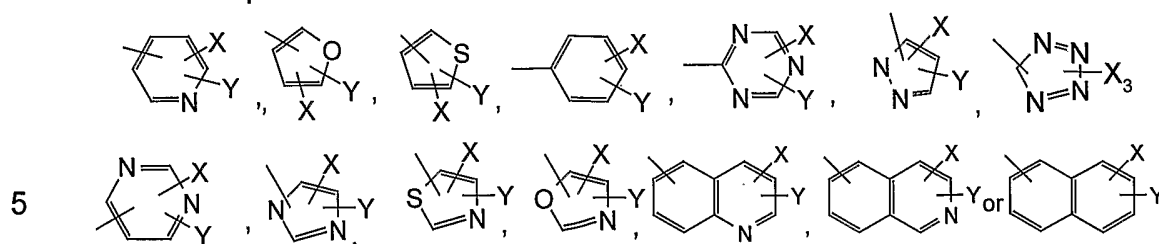
In a variation of formula I R1 and R2 each independently comprise $-(CH_2)_m-Q_1-(CH_2)_n-Z$.

Q_1 comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂

m is an integer from 1 to about 7.

n is an integer from 0 to about 7.

Z comprises



wherein X and Y each independently comprise H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aroyl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aroyl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, alkylsulfonyl, or methylene dioxy when Z comprises a structure having two adjacent carbon atoms.

X₁ and X₂ each independently comprise H or alkyl, or

X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members.

X₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX₁X₂.

In a variation of formula I R₁ and R₂ each independently comprise.

-(CH₂)_m-Q₁-(CH₂)_n-Z.

Q₁ comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

m is an integer from 1 to about 7.

n is an integer from 0 to about 7.

Z comprises an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 4 independently selected

heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members.

In a variation of formula I R1 and R2 each independently comprise

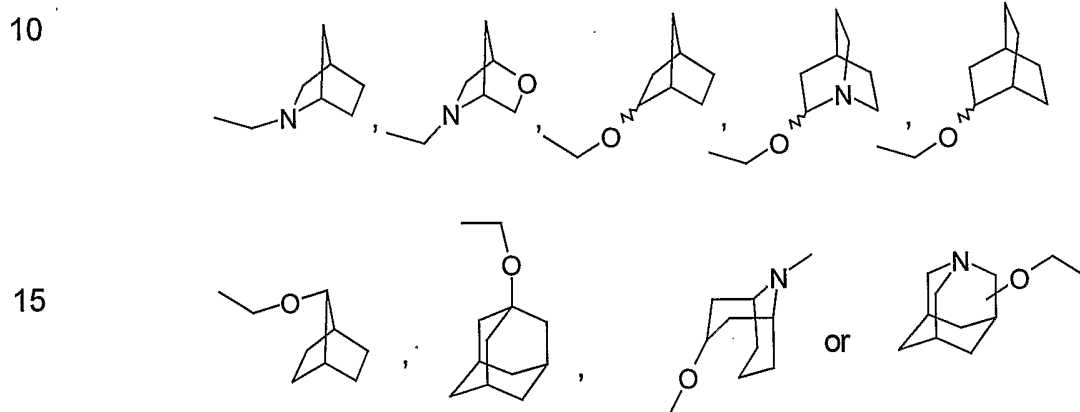
5 $-(CH_2)_m-Q_1-(CH_2)_n-Z$.

Q_1 comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

m is an integer from 1 to about 7.

n is an integer from 0 to about 7.

Z comprises



In a variation of formula I R1 and R2 each independently comprise

20 $-T-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Z comprises H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aroyl, O(CH₂)_jOH, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aroyl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, or alkylsulfonyl.

X₁ and X₂ each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

j is an integer from 0 to about 6.

In a variation of formula I R_1 and R_2 each independently comprise
-T-(CH₂)_n-Z.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the -(CH₂)_n- group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of formula I R1 and R2 each independently comprise $-T-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an
5 unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic
ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having
3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring
members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic
ring, a polycyclic ring or a heteropolycyclic ring.

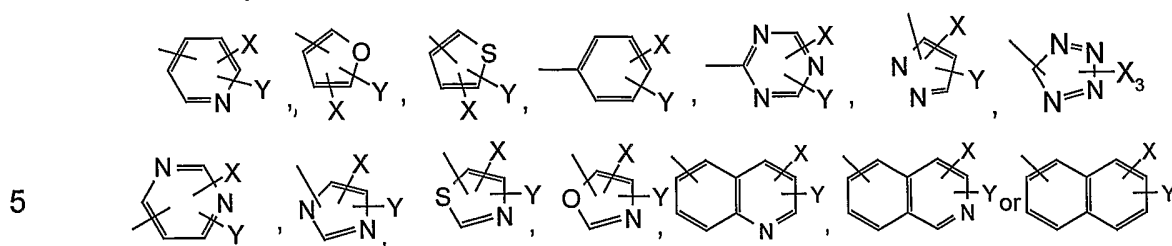
10 Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-
morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl,
2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available
ring atom by an alkyl group; or any above group substituted on at least one
available ring nitrogen atom by a benzyl group, a substituted benzyl group, an
15 alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a
substituted benzhydryl group; and wherein the connecting point between the -
(CH₂)_n- group and the Z group can be any available ring carbon atom or any
available ring nitrogen atom.

20 In a variation of formula I R1 and R2 each independently comprise
 $-T-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an
25 unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic
ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having
3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring
members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic
ring, a polycyclic ring or a heteropolycyclic ring.

Z comprises



wherein X and Y each independently comprise H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms.

X_1 and X_2 each independently comprise H or alkyl, or

15 X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members.

X₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX₁X₂.

20

In a variation of formula I R1 and R2 each independently comprise $-T-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

30 Z comprises an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently

selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 3 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members.

In a variation of formula I R1 and R2 each independently comprise $-T-(CH_2)_n-Q_1-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

10 T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic
15 ring, a polycyclic ring or a heteropolycyclic ring.

Q₁ comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

Z comprises H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aryl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aryl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino or
20 di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X₁ and X₂ each independently comprise H or alkyl, or

X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

25 X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members.

X₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX₁X₂.

j is an integer from 0 to about 6.

30 In a variation of formula I R1 and R2 each independently comprise $-T-(CH_2)_n-Q_1-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Q_1 comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of formula I R1 and R2 each independently comprise $-T-(CH_2)_n-Q_1-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Q_1 comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one

available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any
 5 available ring nitrogen atom.

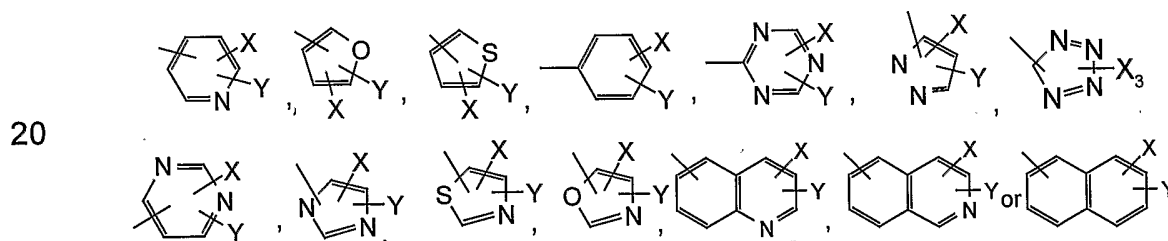
In a variation of formula I R1 and R2 each independently comprise $-T-(CH_2)_n-Q_1-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

10 T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic
 15 ring, a polycyclic ring or a heteropolycyclic ring.

Q_1 comprises N, O, S, $CH=CH$, $C\equiv C$, CO, SO_2 or OSO_2 .

Z comprises



wherein X and Y each independently comprise H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$,
 25 NH-acyl, NH-aryl, CHO, $C(\text{halogen})_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxy when Z comprises a structure having two adjacent carbon atoms.

X_1 and X_2 each independently comprise H or alkyl, or

30 X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

5 In a variation of formula I R_1 and R_2 each independently comprise $-T-(CH_2)_n-Q_1-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

10 T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Q_1 comprises N, O, S, $CH=CH$, $C\equiv C$, CO, SO_2 or OSO_2 .

15 Z comprises an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members or an
20 unsaturated ring having 6 ring atoms and 0 to 3 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members.

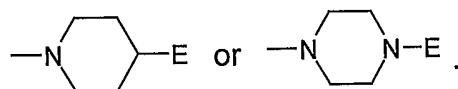
25 In a variation of formula I R_1 and R_2 each independently comprise $-T-(CH_2)_n-Q_1-(CH_2)_n-Z$.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having
30 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

each n independently comprises an integer from 0 to about 7.

Q₁ comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

Z comprises:



5

E comprises a C1 to about C4, linear or branched alkyl group, a phenyl group, a substituted phenyl group, a benzyl group or a substituted benzyl group.

In a variation of formula I R1 and R2 each independently comprise

10 $-T-(CH_2)_n-Q_1-(CH_2)_n-Z$.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

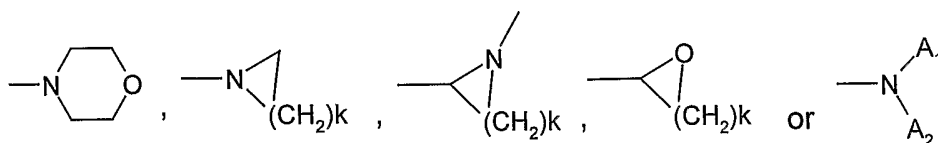
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each n independently comprises an integer from 0 to about 7.

Q₁ comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂

20

Z comprises



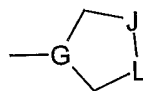
25

k is an integer from 1 to about 5. A₁ and A₂ each independently comprise a C1 to about C4 alkyl group, a phenyl group or a substituted phenyl group.

In a variation of formula I R3 comprises a carbocyclic ring having about 4 to about 7 members, a heterocyclic ring having about 4 to about 7 members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

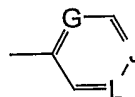
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In a variation of formula I R3 comprises



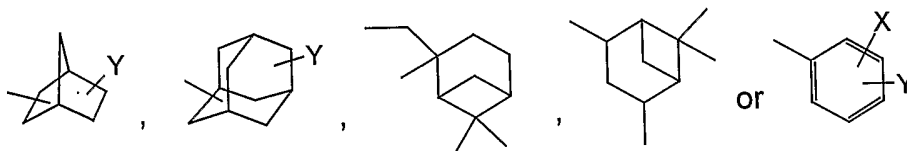
wherein G comprises CH or N, and L and J each independently comprise $(CH_2)_n$, O, NH or S. n is an integer from 0 to about 7.

In a variation of formula I R3 comprises



wherein G, L and J each independently comprise CH or N.

In a variation of formula I R3 comprises



wherein X and Y each independently comprise H, halogen, N_3 , NCS, phenyl, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members).

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

j is 0 to about 6.

In a variation of formula I R3 comprises a carbocyclic ring having 4 to 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a carbocyclic ring

having 4 to 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heteroaromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms or a heteroaromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms.

10

In a variation of formula I R₄ comprises H, halogen, N₃, NCS, phenyl, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aryl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aryl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl, or alkylsulfonyl.

15

X₁ and X₂ each independently comprise H or alkyl, or

X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members).

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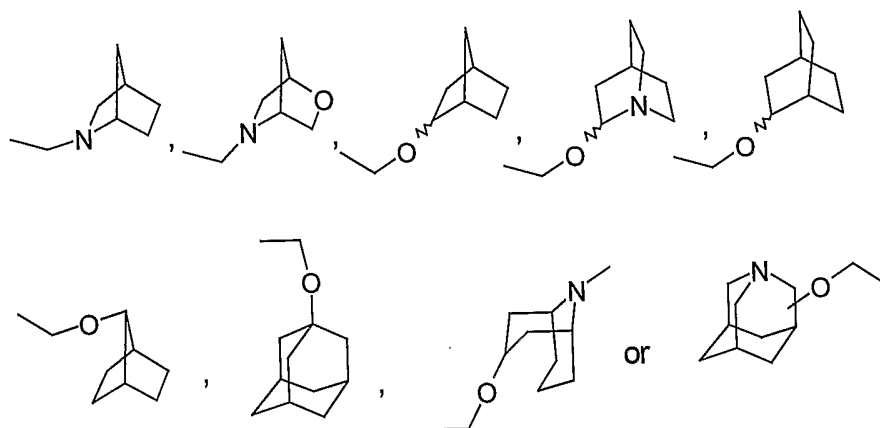
X₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX₁X₂.

j is an integer from 0 to about 6.

In a variation of formula I R₄ comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

30

In an advantageous variation of formula I R4 comprises



In a variation of formula I R4 comprises $-(CH_2)_d-Z$.

d is an integer from 1 to about 6.

Z comprises H, halogen, N_3 , NCS, phenyl, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aroyl, $O(CH_2)_jOH$, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aroyl, CHO, C(halogen) $_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members).

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

j is an integer from 0 to about 6.

In a variation of formula I R4 comprises $-CH_2OH$ or $-CH_2Oalkyl$.

In a variation of formula I R4 comprises $-(CH_2)_d-Z$.

d is an integer from 1 to about 6.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7

ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_d-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

10 In a variation of formula I R4 comprises $-(CH_2)_d-Z$.

d is an integer from 1 to about 6.

Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_d-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of formula I R4 comprises $-(CH_2)_m-Q_1-(CH_2)_n-Z$.

Q_1 comprises N, O, S, $CH=CH$, $C\equiv C$, CO, SO_2 or OSO_2 .

m is an integer from 1 to about 7.

25 n is an integer from 0 to about 7.

Z comprises H, halogen, N_3 , NCS, phenyl, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alkoxy, alkylmercapto, alkylamino, dialkylamino, alkylsulfinyl or alkylsulfonyl.

30 X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

j is an integer from 0 to about 6.

5

In a variation of formula I R_4 comprises $-(CH_2)_m - Q_1 - (CH_2)_n - Z$.

Q_1 comprises N, O, S, $CH=CH$, $C\equiv C$, CO, SO_2 or OSO_2 .

m is an integer from 1 to about 7.

n is an integer from 0 to about 7.

10

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members; a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

15

20

In a variation of formula I R_4 comprises $-(CH_2)_m - Q_1 - (CH_2)_n - Z$.

Q_1 comprises N, O, S, $CH=CH$, $C\equiv C$, CO, SO_2 or OSO_2 .

m is an integer from 1 to about 7.

25

n is an integer from 0 to about 7.

Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group

30

and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

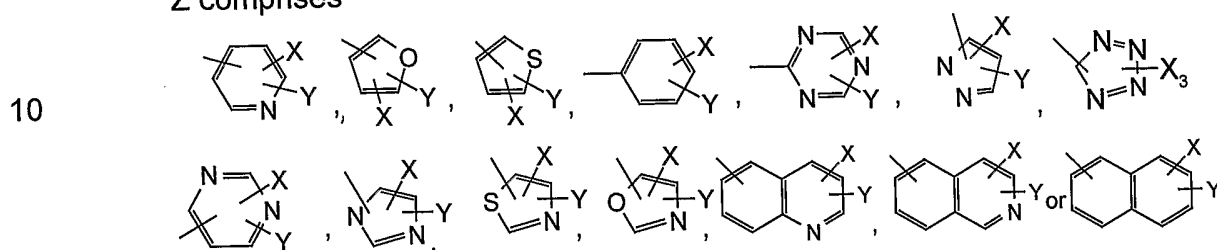
In a variation of formula I R₄ comprises $-(CH_2)_m - Q_1 - (CH_2)_n - Z$.

Q₁ comprises N, O, S, CH=CH, C≡C, CO, SO₂ or OSO₂.

m is an integer from 1 to about 7.

n is an integer from 0 to about 7.

Z comprises



wherein X and Y each independently comprise H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aryl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aryl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or methylene dioxo when Z comprises a structure having two adjacent carbon atoms.

X₁ and X₂ each independently comprise H or alkyl, or

X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members.

X₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX₁X₂.

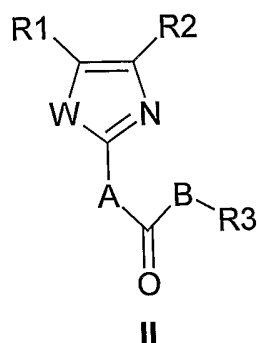
J is an integer from 0 to about 6.

In any variation of formula I, when A is a direct bond; and B is N(R₅); and either of R₁ and R₂ is phenyl [optionally substituted with one more halogen atoms, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆) alkyl

sulfonyl, (C₁-C₆) alkyl sulfonyl amino, (C₁-C₆) alkyl carbonyl-amino, (C₁-C₆) alkyl amino-carbonyl-amino or phenyl], (C₂-C₆) alkyl, cyclohexyl [optionally substituted with (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, cyano or one or more fluorine atoms], 1-naphthyl or 2-naphthyl [optionally substituted with one or more halogen atoms], 5 atoms, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl or cyano], benzyl [optionally substituted on the phenyl ring with one or more halogen atoms, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl or cyano], a 5- to 10-membered saturated or unsaturated heterocyclic radical [optionally substituted with one or more fluorine atoms, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl or cyano] and a 5- to 10-
10 membered aromatic monocyclic or bicyclic heterocyclic radical [optionally substituted with one more halogen atoms, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, cyano, nitro or phenyl] and R₃ is any above described variation; then R₄ can not be H, (C₁-C₆) alkyl, benzyl, chloro, or bromo.

15 In any variation of formula I when A is a direct bond; and B is N(R₅); and either R₁ or R₂ is phenyl, thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl or any above group substituted with 1, 2, 3 or 4 substituents which can be the same or different, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy,
20 nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkoxycarbonyl, carboxyl, cyano, carbonyl, acetyl and naphthyl; and R₃ is any above described variation; then R₄ can not be H, halogen, CN, carbonyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfanyl, branched or unbranched C₁₋₄ alkyl group, which C₁₋₄ alkyl group
25 may be substituted with 1 to 3 fluoro atoms or with a single bromo, chloro, iodo, cyano or hydroxy group.

Another embodiment of the invention comprises cannabimimetic thiazole and oxazole ligands represented by formula II:



10 wherein A, B, R1, R2 and R3 are as defined above for compounds of formula I.

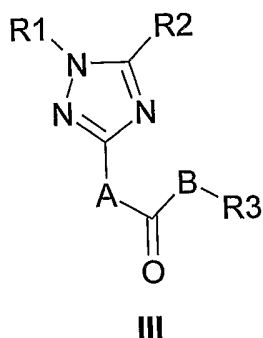
W comprises S or O.

15 In any variation of formula II, when A is a direct bond; B is NR⁵ as defined above; R1 and R3 are any above described variation; and W is S; then R2 cannot be a phenyl group with one or more substituents selected from branched or unbranched C₁₋₃-alkyl, branched or unbranched C₁₋₃-alkoxy, hydroxy, halogen, CF₃, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono-or dialkyl(C₁₋₂)-

20 amino, mono-or dialkyl(C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, branched or unbranched (C₁₋₃)-sulfonyl, carboxyl, cyano, carbamoyl, branched or unbranched dialkyl(C₁₋₃)-aminosulfonyl, branched or unbranched monoalkyl(C₁₋₃)-aminosulfonyl and acetyl.

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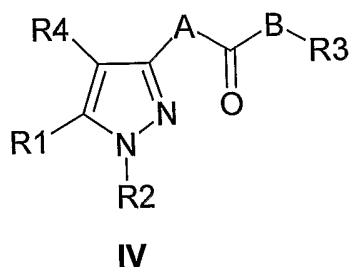
Another embodiment of the invention comprises cannabimimetic triazole ligands represented by formula III:



10 wherein A, B, R1, R2 and R3 are as defined above for compounds of formula I.

In any variation of formula III, when A is a direct bond; B is NR₅; R₃ is any above described variation; then either or both of R₁ and R₂ cannot be a phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, or triazinyl group, or any
 15 above group substituted with 1-4 substituents, which can be same or different, selected from branched or unbranched (C₁₋₃)alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkoxycarbonyl,
 20 trifluoromethylsulfonyl, sulfomyl, (C₁₋₃)-alkylsulfonyl, carboxyl, cyano, carbonyl, (C₁₋₃)-dialkylaminosulfonyl, (C₁₋₃)-monoalkylamino-sulfonyl and acetyl.

Another embodiment of the invention comprises cannabimimetic pyrazole ligands represented by formula IV:



30 wherein A, B, R2, R3 and R4 are as defined above for compounds of formula I.

In a variation of formula IV R1 comprises $-T-(CH_2)_n-Q-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an
 5 unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic
 ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having
 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring
 members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic
 ring, a polycyclic ring or a heteropolycyclic ring.

10 Q is optionally present and if present comprises $CH=CH$, $C\equiv C$.

Z comprises H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-
 aroyl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aroyl, $NHC(O)-O-X_3$, CHO,
 $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, SX_1 , $Si(X_1)_3$, alkoxy,
 alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

15 X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about
 4 to about 7 ring members and optionally one additional heteroatom
 selected from O, N or S, or

20 X_1 and X_2 together comprise part of an imide ring having about 5 to
 about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

each j is independently an integer from 0 to about 6.

In a variation of formula IV R1 comprises $-T-(CH_2)_n-Q-(CH_2)_n-Z$.

25 each n independently comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an
 unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic
 ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having
 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring
 30 members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic
 ring, a polycyclic ring or a heteropolycyclic ring.

Q is optionally present and if present comprises CH=CH, C≡C.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of formula IV R1 comprises $-T-(CH_2)_n-Q-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Q is optionally present and if present comprises CH=CH, C≡C.

Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

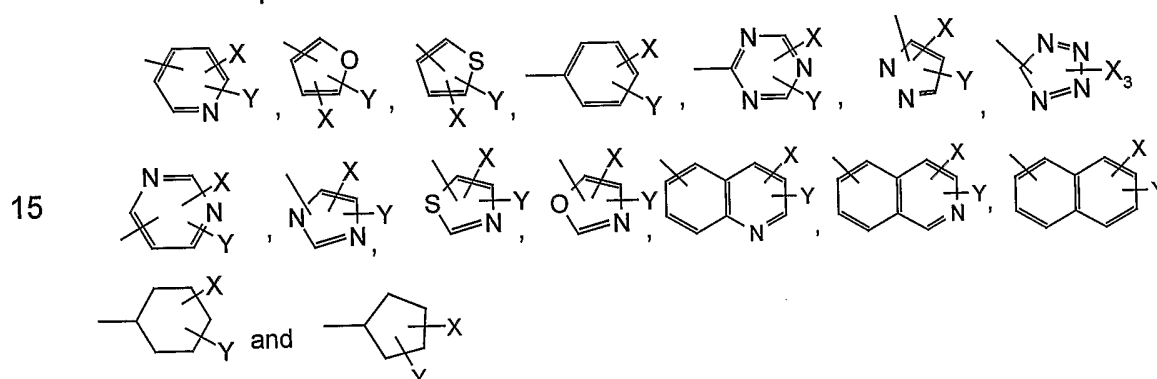
In a variation of formula IV R1 comprises $-T-(CH_2)_n-Q-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an
 5 unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic
 ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having
 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring
 members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic
 ring, a polycyclic ring or a heteropolycyclic ring.

10 Q is optionally present and if present comprises $CH=CH$, $C\equiv C$.

Z comprises



20 CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aroyl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$,
 NH-acyl, NH-aroyl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$,
 $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino or di-
 alkylamino, alkylsulfinyl, alkylsulfonyl, or methylene dioxy when Z
 comprises a structure having two adjacent carbon atoms.

25 X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having
 about 4 to about 7 ring members and optionally one additional
 heteroatom selected from O, N or S, or

30 X_1 and X_2 together comprise part of an imide ring having
 about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl- NX_1X_2 .

j is an integer from 0 to about 6.

In a variation of formula IV R1 comprises $-T-(CH_2)_n-Q-(CH_2)_n-Z$.

each n independently comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Q is optionally present and if present comprises $CH=CH$, $C\equiv C$.

10 Z comprises an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members or an
15 unsaturated ring having 6 ring atoms and 0 to 3 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members

20 In a variation of formula IV R1 comprises $-T-(CH_2)_n-Q-(CH_2)_n-Z$.

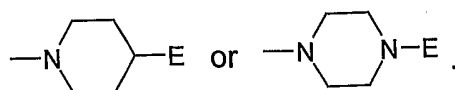
T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring
25 members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

each n independently comprises an integer from 0 to about 7.

Q is optionally present and if present comprises $CH=CH$, $C\equiv C$.

30

Z comprises



E comprises a C1 to about C4, linear or branched alkyl group, a phenyl group, a substituted phenyl group, a benzyl group or a substituted benzyl group.

5 In a variation of formula IV R1 comprises $-T-(CH_2)_n-Q-(CH_2)_n-Z$.

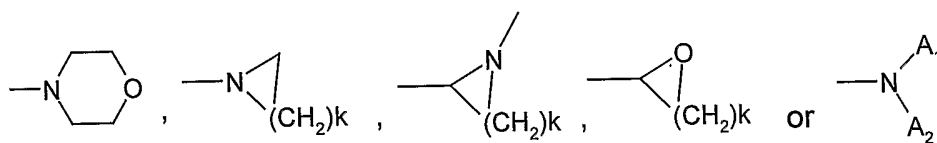
T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

each n independently comprises an integer from 0 to about 7.

Q is optionally present and if present comprises $CH=CH$, $C\equiv C$.

Z comprises

15



20

k is an integer from 1 to about 5. A_1 and A_2 each independently comprise a C1 to about C4 alkyl group, a phenyl group or a substituted phenyl group.

The inventive compounds in any formula, embodiment or variation include any and all possible isomers and stereoisomers. In general, the compositions of the invention may be alternately formulated to comprise, consist of, or consist essentially of, any appropriate components herein disclosed. The compositions of the invention may additionally, or alternatively, be formulated so as to be devoid, or substantially free, of any components, materials, ingredients, adjuvants or species used in the prior art compositions or that are otherwise not necessary to the achievement of the function and/or objectives of the present invention.

Unless otherwise specifically defined, "acyl" refers to the general formula $-C(O)alkyl$.

Unless otherwise specifically defined, "acyloxy" refers to the general formula -O-acyl .

Unless otherwise specifically defined, "alcohol" refers to the general formula alkyl-OH and includes primary, secondary and tertiary variations.

5 Unless otherwise specifically defined, "alkyl" or "lower alkyl" refers to a linear, branched or cyclic alkyl group having from 1 to about 10 carbon atoms, and advantageously 1 to about 7 carbon atoms including, for example, methyl, ethyl, propyl, butyl, hexyl, octyl, isopropyl, isobutyl, tert-butyl, cyclopropyl, cyclohexyl, cyclooctyl, vinyl and allyl. The alkyl group can be saturated or unsaturated. The
10 alkyl group can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. Unless otherwise specifically limited, a cyclic alkyl group includes monocyclic, bicyclic, tricyclic, tetracyclic and polycyclic rings, for example norbornyl, adamantyl and related terpenes.

15 Unless otherwise specifically defined, "alkoxy" refers to the general formula -O-alkyl .

Unless otherwise specifically defined, "alkylmercapto" refers to the general formula -S-alkyl .

20 Unless otherwise specifically defined, "alkylamino" refers to the general formula -(NH)-alkyl .

Unless otherwise specifically defined, "di-alkylamino" refers to the general formula -N-(alkyl)_2 . Unless otherwise specifically limited di-alkylamino includes cyclic amine compounds such as piperidine and morpholine.

25 Unless otherwise specifically defined, an aromatic ring is an unsaturated ring structure having about 5 to about 7 ring members and including only carbon as ring atoms. The aromatic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

30 Unless otherwise specifically defined, "aryl" refers to an aromatic ring system that includes only carbon as ring atoms, for example phenyl, biphenyl or naphthyl. The aryl group can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "aroyl" refers to the general formula -C(=O)-aryl .

Unless otherwise specifically defined, a bicyclic ring structure comprises 2 fused or bridged rings that include only carbon as ring atoms. The bicyclic ring structure can be saturated or unsaturated. The bicyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of bicyclic ring structures include naphthalene and bicyclooctane.

Unless otherwise specifically defined, a carbocyclic ring is a non-aromatic ring structure, saturated or unsaturated, having about 3 to about 8 ring members that includes only carbon as ring atoms, for example, cyclohexadiene or cyclohexane. The carbocyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "halogen" refers to an atom selected from fluorine, chlorine, bromine and iodine.

Unless otherwise specifically defined, a heteroaromatic ring is an unsaturated ring structure having about 5 to about 8 ring members independently selected from carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, for example, pyridine, furan, quinoline, and their derivatives. The heteroaromatic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, a heterobicyclic ring structure comprises 2 fused or bridged rings having ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur. The heterobicyclic ring structure can be saturated or unsaturated. The heterobicyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heterobicyclic ring structures include isobenzofuran and indole.

Unless otherwise specifically defined, a heterocyclic ring is a saturated or unsaturated ring structure having about 3 to about 8 ring members independently selected from carbon atoms and one or more heteroatoms, including oxygen,

nitrogen and/or sulfur; for example, piperidine, morpholine, piperazine, pyrrolidine, thiomorpholine, and their derivatives. The heterocyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

5 Unless otherwise specifically defined, a heterotricyclic ring structure comprises 3 fused, bridged, or both fused and bridged rings having ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur. The heterotricyclic ring structure may be saturated or unsaturated. The heterotricyclic ring structure can be unsubstituted, singly
10 substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heterotricyclic ring structures include carbazole, phenanthroline, phenazine, 2,4,10-trioxaadamantane and tetradecahydro-phenanthroline.

Unless otherwise specifically defined, a heteropolycyclic ring structure
15 comprises more than 3 rings that may be fused, bridged or both fused and bridged and that have ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur. The heteropolycyclic ring structure can be saturated or unsaturated. The heteropolycyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with
20 substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heteropolycyclic ring structures include azaadamantine, tropane, homotropene and 5-norbornene-2,3-dicarboximide.

Unless otherwise specifically defined, the term "phenacyl" refers to the general formula –phenyl–acyl.

25 Unless otherwise specifically defined, a polycyclic ring structure comprises more than 3 rings that may be fused, bridged or both fused and bridged, and that includes carbon as ring atoms. The polycyclic ring structure can be saturated or unsaturated. The polycyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible
30 position. The individual rings may or may not be of the same type. Examples of polycyclic ring structures include adamantane, bicyclooctane, norbornane and bicyclononanes.

Unless otherwise specifically defined, a spirocycle refers to a ring system wherein a single atom is the only common member of two rings. A spirocycle can comprise a saturated carbocyclic ring comprising about 3 to about 8 ring members, a heterocyclic ring comprising about 3 to about 8 ring atoms wherein up to about 3 ring atoms may be N, S, or O or a combination thereof.

Unless otherwise specifically defined, a tricyclic ring structure comprises 3 rings that may be fused, bridged or both fused and bridged, and that includes carbon as ring atoms. The tricyclic ring structure can be saturated or unsaturated. The tricyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. and may be substituted or unsubstituted. The individual rings may or may not be of the same type. Examples of tricyclic ring structures include fluorene and anthracene.

Unless otherwise specifically limited the term substituted means substituted by a below-described substituent group in any possible position. Substituent groups for the above moieties useful in the invention are those groups that do not significantly diminish the biological activity of the inventive compound. Substituent groups that do not significantly diminish the biological activity of the inventive compound include, for example, H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, C(X₃)₃, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, NHCOalkyl, CHO, C(halogen)₃, COOX₃, SO₃H, PO₃H₂, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, sulfonamide, thioalkoxy or methylene dioxy when the substituted structure has two adjacent carbon atoms, wherein X₁ and X₂ each independently comprise H or alkyl, or X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members and X₃ comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX₁X₂. Unless otherwise specifically limited a substituent group may be in any possible position.

Some of the inventive compounds show a high affinity for at least one of the cannabinoid receptors. Thus, another aspect of the invention is use of at least one of the inventive compounds to interact with a cannabinoid receptor.

Some of the novel imidazole derivatives show selectivity for the CB1 cannabinoid receptor. These inventive CB1 selective analogs are able to interact with the CB1 cannabinoid receptor without affecting the peripheral (CB2) receptor

to the same degree. Therefore, still another aspect of the invention is use of at least one of the inventive compounds to preferentially interact with a CB1 cannabinoid receptor.

The inventive imidazole analogs described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response. Thus, another aspect of the invention is the administration of a therapeutically effective amount of at least one of the inventive compounds, or a physiologically acceptable salt thereof, to an individual or animal to provide a physiological response.

A better understanding of the invention will be obtained from the following detailed description of the article and the desired features, properties, characteristics, and the relation of the elements as well as the process steps, one with respect to each of the others, as set forth and exemplified in the description and illustrative embodiments.

Detailed Description

As used herein a "therapeutically effective amount" of a compound, is the quantity of a compound which, when administered to an individual or animal, results in a sufficiently high level of that compound in the individual or animal to cause a physiological response, for example a discernible increase or decrease in stimulation of cannabinoid receptors. The inventive compounds described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response useful to treat marijuana abuse, obesity, schizophrenia, epilepsy, stress, memory disorders, migraine, vomiting, thymic disorders, dyskinesia, kinetic disorder, anxiety disorders, psychotic disorders, cognitive disorders, appetite disorders, mood disorders, delirious disorders, neuropathies, Parkinson's disease, Alzheimers disease, depression, psychosomatic-induced disease, as well as for alcohol, opioid, nicotine and cocaine addiction, etc. Additionally, these analogs can be useful in cancer chemotherapy. Typically, a "therapeutically effective amount" of an inventive compound is believed to range from about 10 mg/day to about 1,000 mg/day.

As used herein, an "individual" refers to a human. An "animal" refers to, for example, veterinary animals, such as dogs, cats, horses and the like, and farm animals, such as cows, pigs and the like.

The compound of the present invention can be administered by a variety of known methods, including orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration. Such forms include, but are not limited to, capsular and tablet formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular, subcutaneous, ocular, intranasal, inhalation-based and transdermal administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically acceptable vehicles include, for example, saline, sterile water, Ringer's solution and isotonic sodium chloride solutions. The specific dosage level of active ingredient will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

The following examples are given for purposes of illustration only in order that the present invention may be more fully understood. These examples are not intended to limit in any way the scope of the invention unless otherwise specifically indicated.

Examples:

A number of inventive cannabimimetic imidazole and pyrazole derivatives were prepared. Table 1 illustrates some prepared CB1 selective imidazole analogs (compounds 1-1 to 1-41). Table 2 illustrates some prepared CB1 selective pyrazole analogs (compounds 2-1 to 2-3). Tables 3 to 5 illustrate some other disclosed compounds (3-1 to 3-12; 4-1 to 4-7; and 5-1 to 5-21).

Table 1

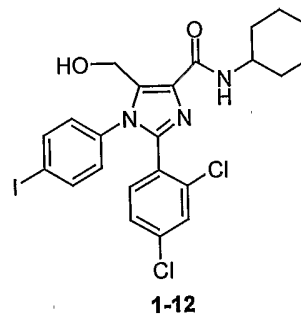
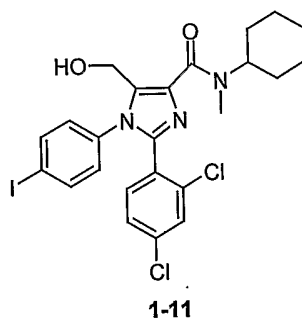
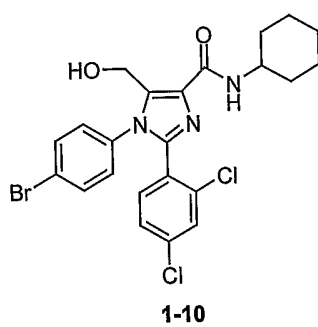
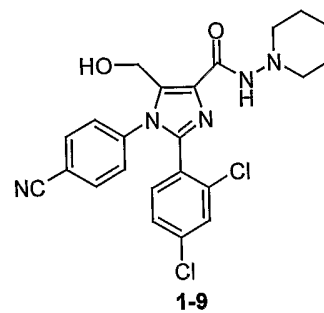
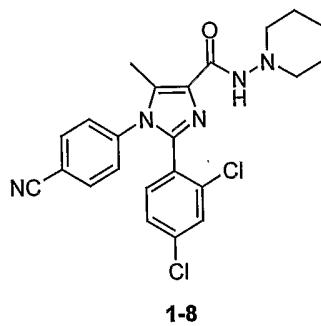
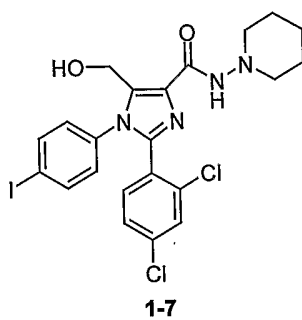
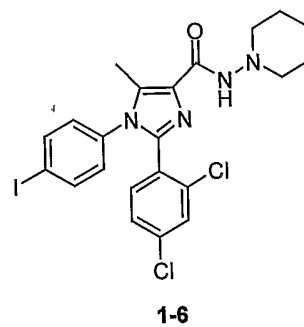
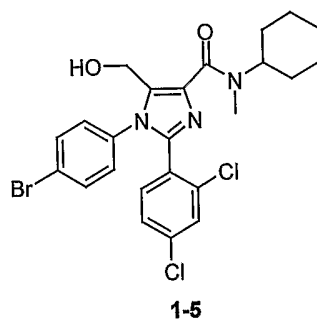
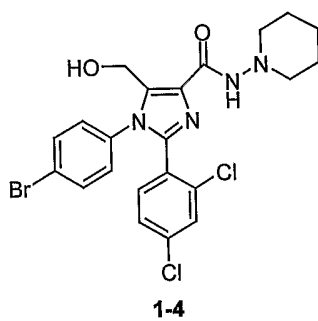
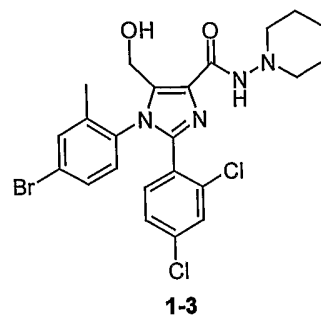
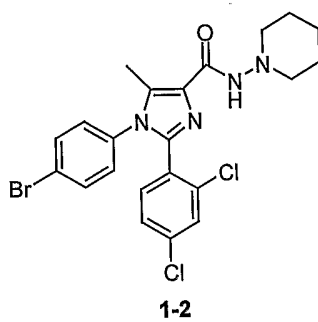
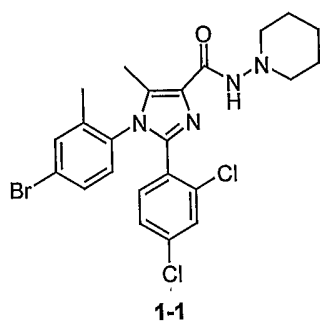


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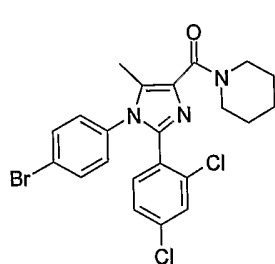
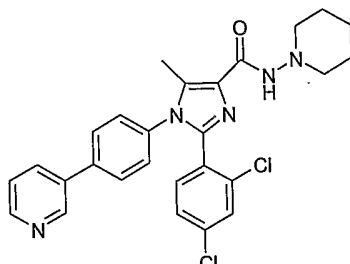
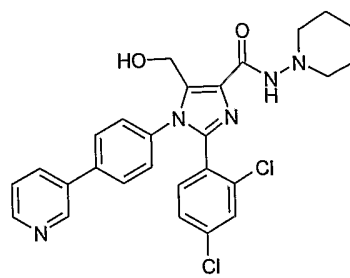
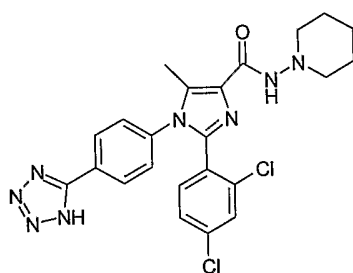
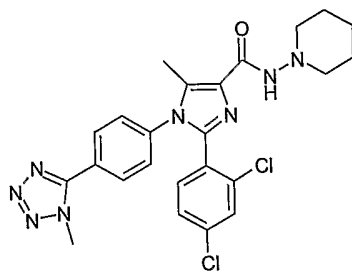
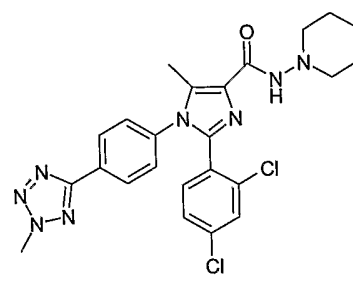
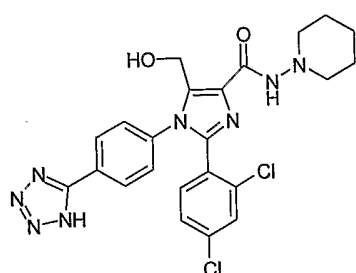
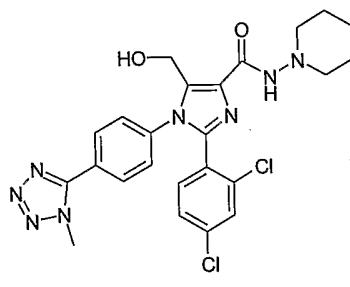
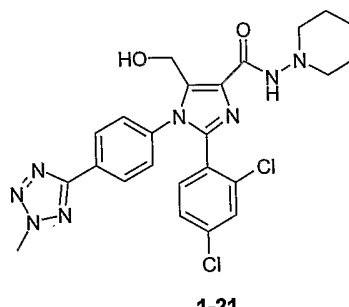
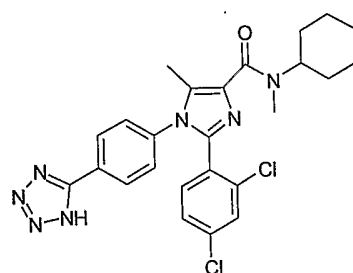
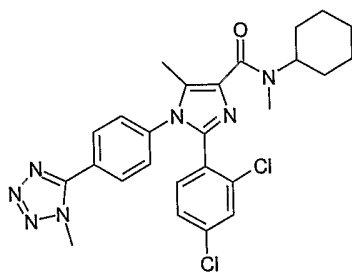
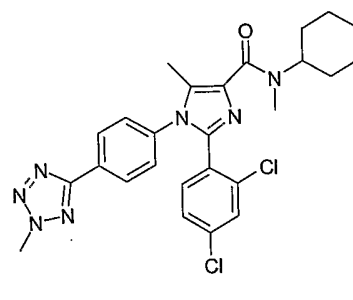
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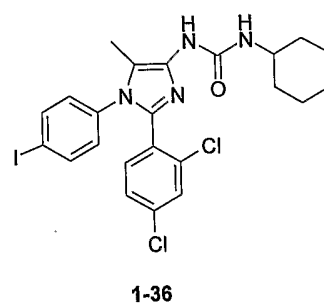
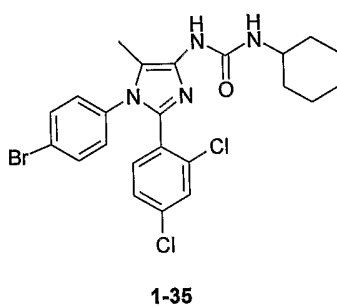
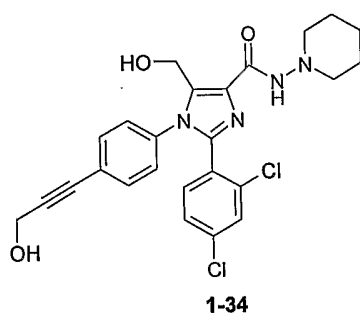
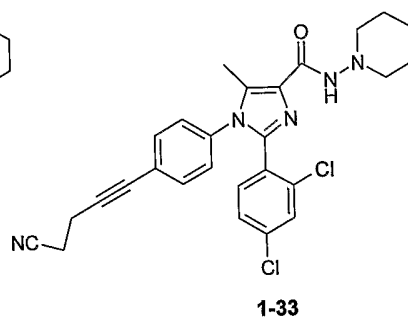
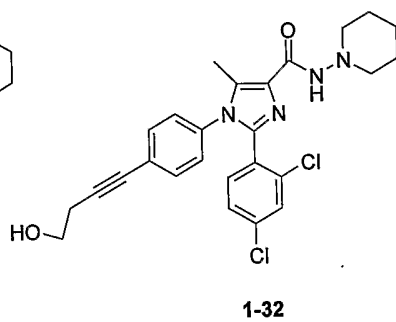
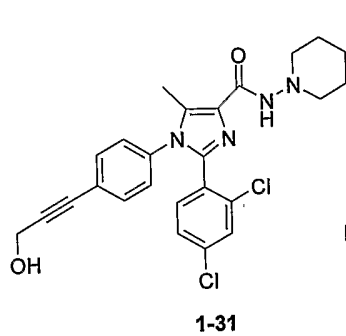
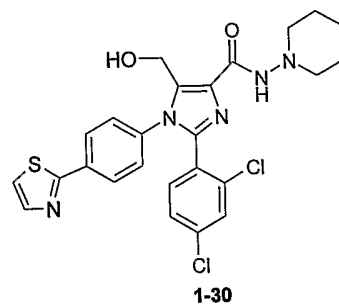
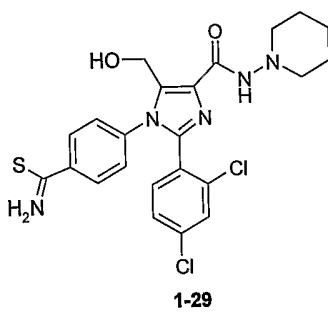
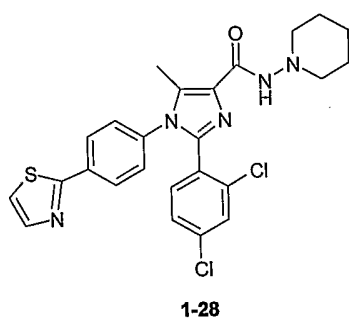
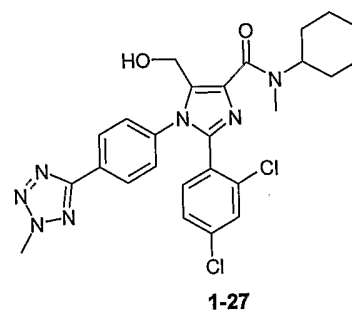
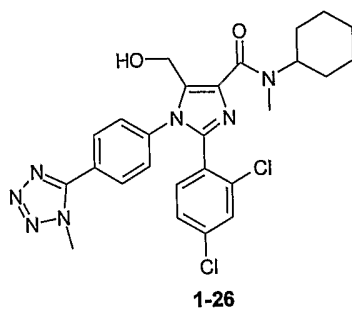
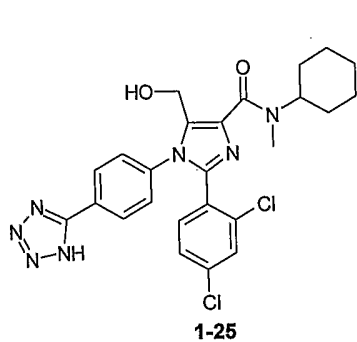


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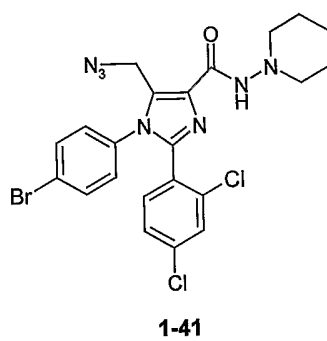
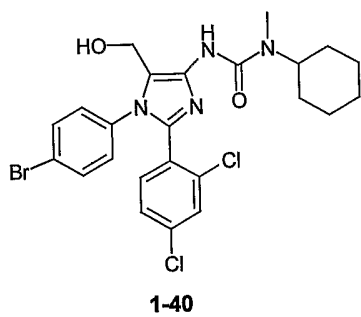
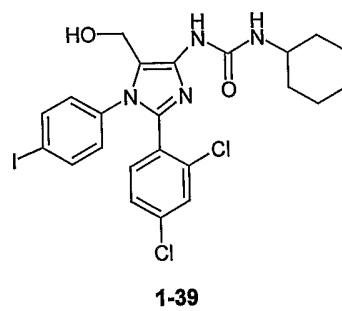
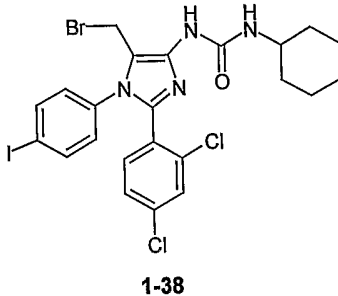
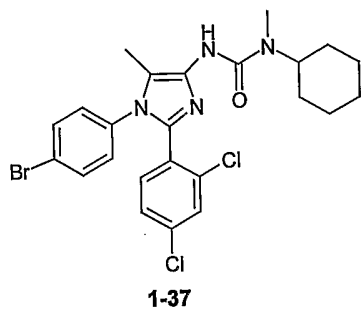


Table 2

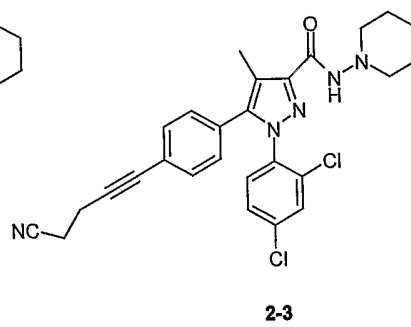
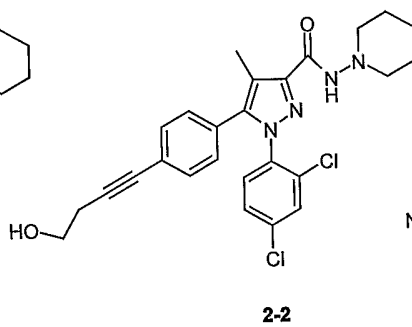
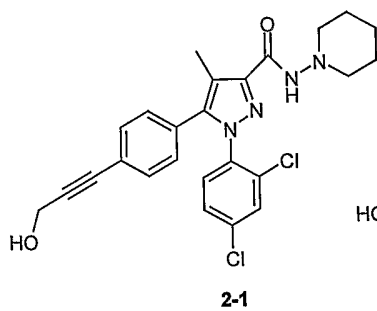


Table 3

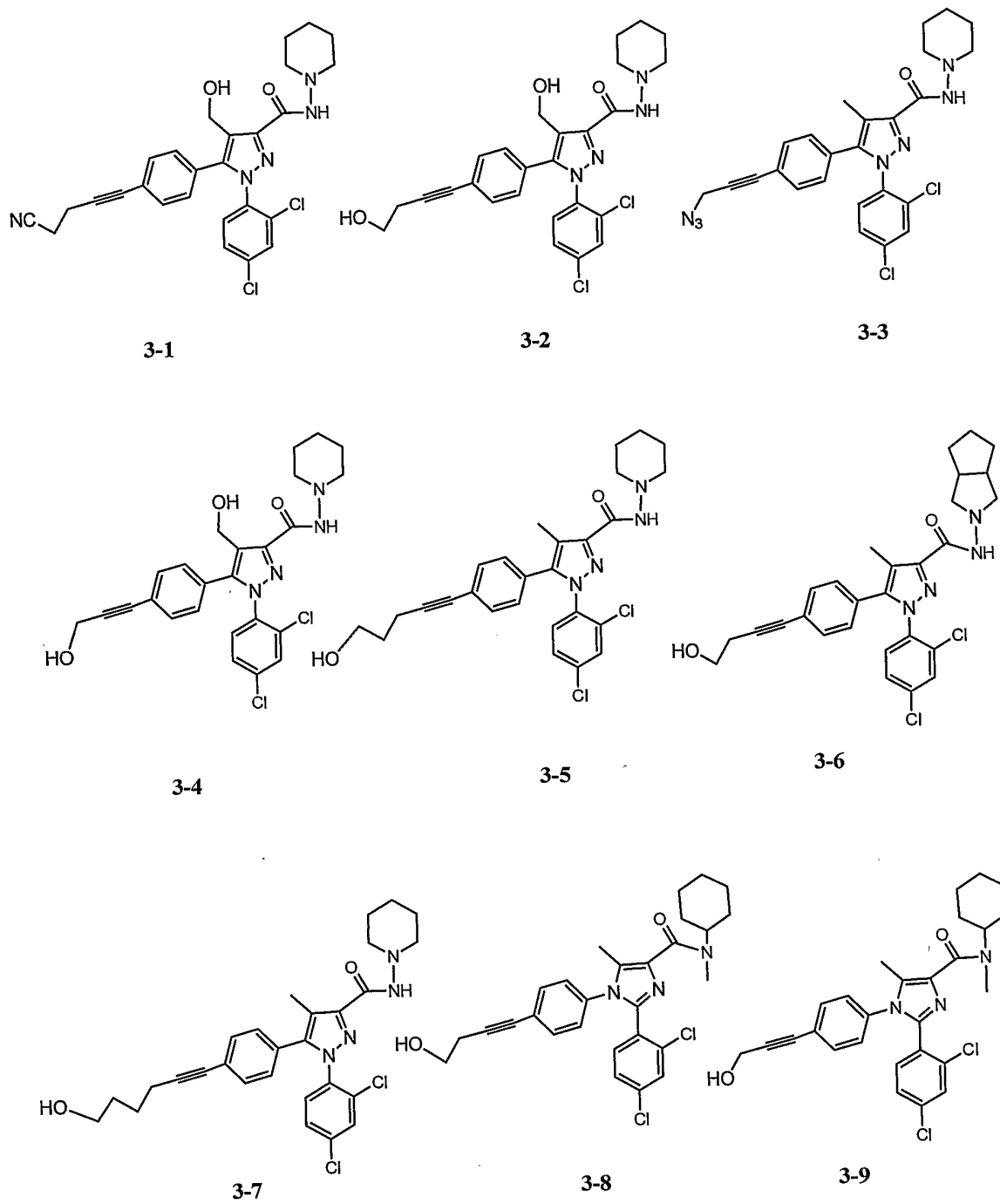


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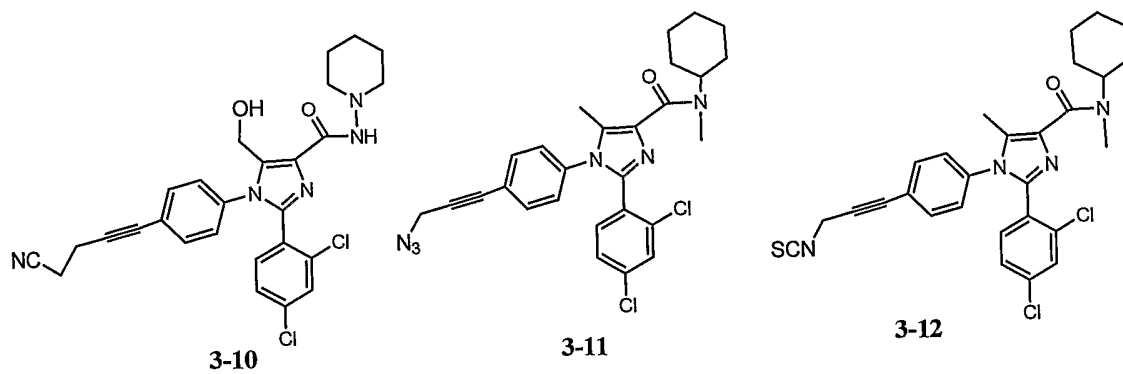


Table 4

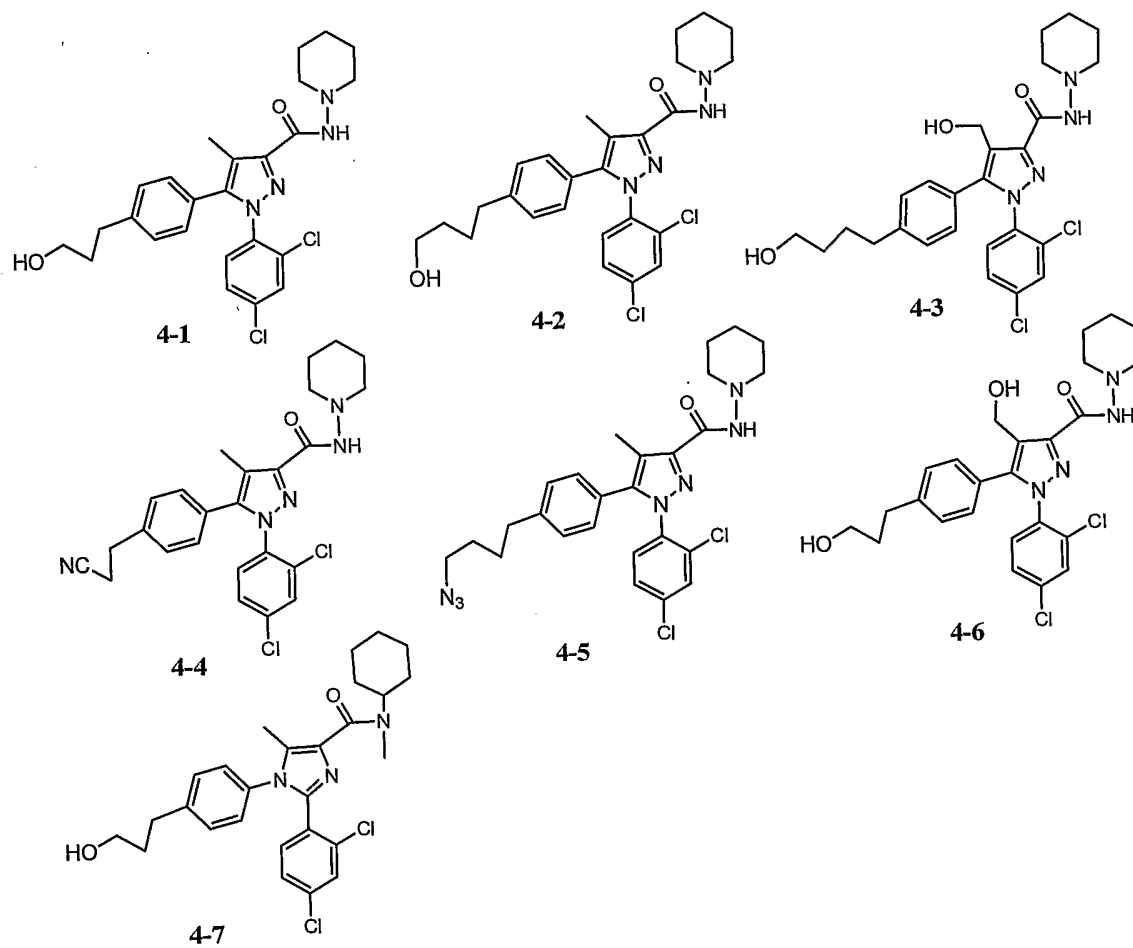


Table 5

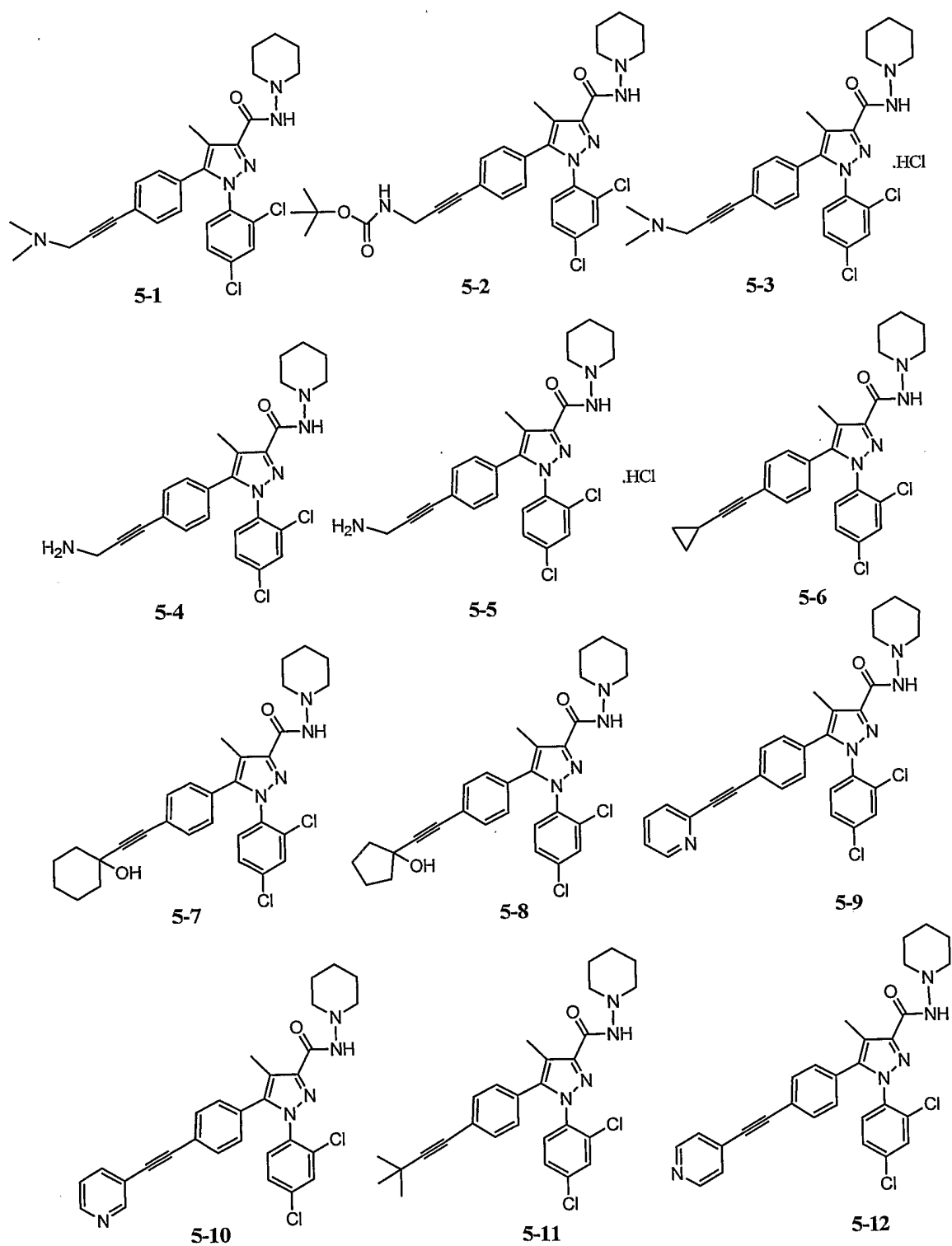
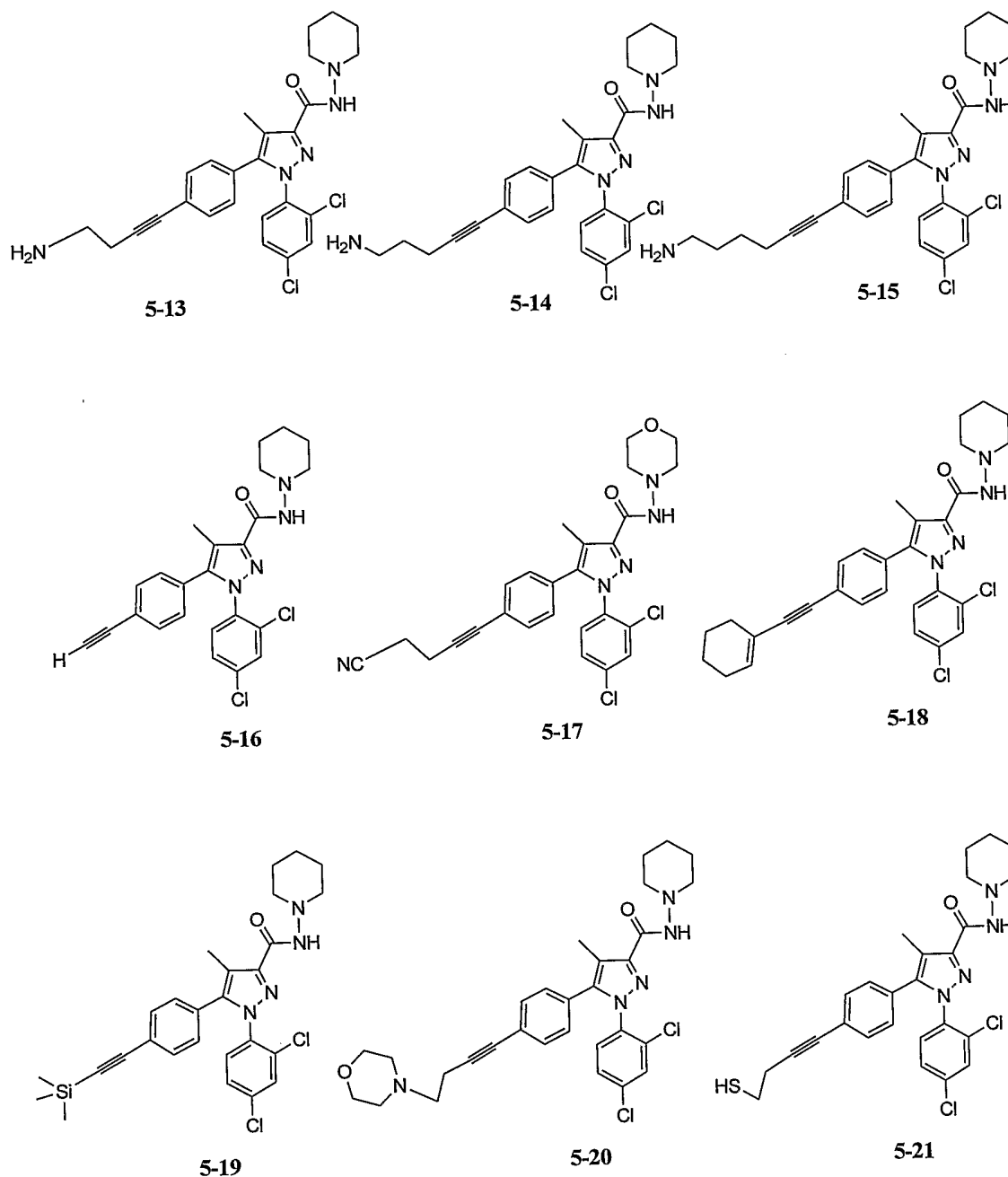


Table 5 (continued)



5 Some of the inventive analogs were tested for CB2 receptor binding affinity and for CB1 receptor affinity (to determine selectivity). As used herein, "binding affinity" is represented by the K_i value which is the inhibition constant correlated with the concentration of an analog required to occupy the 50% of the total number (B_{max}) of the receptors. The lower the K_i value the higher the binding
10 affinity. As used herein an analog is said to have "binding selectivity" if it has

higher binding affinity for one receptor compared to the other receptor; e.g. a cannabinoid analog which has a K_i of 0.1 nM for CB1 and 10 nM for CB2, is 100 times more selective for the CB1 receptor.

For the CB1 receptor binding studies, membranes were prepared from rat
5 forebrain membranes according to the procedure of P. R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 107 - 118 (1981). The binding of the novel analogues to the CB1 cannabinoid receptor was assessed as described in W. A. Devane et al, Determination and Characterization of a Cannabinoid Receptor in a Rat Brain,
10 Mol. Pharmacol., 34, 605 - 613 (1988) and A. Charalambous et al, 5'-azido Δ^8 -THC: A Novel Photoaffinity Label for the Cannabinoid Receptor, J. Med. Chem., 35, 3076 - 3079 (1992) with the following changes. The above articles are incorporated by reference herein.

Membranes, previously frozen at -80°C , were thawed on ice. To the stirred
15 suspension was added three volumes of TME (25 mM Tris-HCl buffer, 5 mM MgCl_2 and 1 mM EDTA) at a pH 7.4. The suspension was incubated at 4°C for 30 min. At the end of the incubation, the membranes were pelleted and washed three times with TME.

The treated membranes were subsequently used in the binding assay
20 described below. Approximately 30 μg of membranes were incubated in silanized 96-well microtiter plate with TME containing 0.1% essentially fatty acid-free bovine serum albumin (BSA), 0.8 nM $[^3\text{H}]$ CP-55,940, and various concentrations of test materials in a final volume of 200 μL . The assays were incubated for 1 hour at 30°C and then immediately filtered using Packard Filtermate 196 harvester and
25 Whatman GF/C filterplates and washed with wash buffer (TME) containing 0.5% BSA. Radioactivity was detected using MicroScint 20 scintillation cocktail added directly to the dried filterplates, and the filterplates were counted using a Packard Instruments Top-Count. Nonspecific binding was assessed using 100 nM CP-55,940. Data collected from three independent experiments performed with
30 duplicate determinations was normalized between 100% and 0% specific binding for $[^3\text{H}]$ CP-55,940, determined using buffer and 100 nM CP-55,940. The normalized data was analyzed using a 4-parameter nonlinear logistic equation to yield IC_{50} values. Data from at least two independent experiments performed in

duplicate was used to calculate IC_{50} values which were converted to K_i values using the assumptions of Cheng et al, Relationship Between the Inhibition Constant (K_i) and the concentration of Inhibitor which causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction, Biochem. Pharmacol., 22, 3099-3102, (1973), which is

5 incorporated by reference herein.

For the CB2 receptor binding studies, membranes were prepared from frozen mouse spleen essentially according to the procedure of P. R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 226, 107 - 118 (1981) which is incorporated by reference
10 herein. Silanized centrifuge tubes were used throughout to minimize receptor loss due to adsorption. The CB2 binding assay was conducted in the same manner as for the CB1 binding assay. The binding affinities (K_i) were also expressed in nanomoles (nM).

For the compounds of Table 1 the CB1 cannabinoid receptor binding
15 affinities (K_i) for the synthesized analogs range between 1.2 and 5762. The CB2 cannabinoid receptor binding affinities (K_i) for the synthesized analogs range between 75.3 and 26311. The CB1 cannabinoid receptor selectivity for some of the synthesized analogs range from about 2 to about 452. The CB2 cannabinoid receptor selectivity for some of the synthesized analogs range from about 1 to
20 about 4. The cannabinoid receptor binding affinities (K_i) for the synthesized analogs of Table 1 are summarized in Table 6.

Table 6		
Compound no.	CB1 K_i	CB2 K_i
1-1	29.8	808.2
1-2	11.5	462.1
1-3	54.7	803.3
1-4	10.8	318.6
1-5	28.8	3784
1-6	2.7	4309
1-7	1.5	1645
1-8	57	7222
1-9	51	5465
1-10	4.6	3032
1-11	6.4	1148
1-12	19	22433
1-13	22	2454

Table 6		
Compound no.	CB1 Ki	CB2 Ki
1-14	39.8	3329
1-15	23	2781
1-16	404	10714
1-17	2285	24509
1-18	6.5	5082
1-19	5762	22315
1-20	400	12269
1-21	10.5	539
1-22	359	26311
1-23	982	4145
1-24	11.2	220
1-25	5214	858.2
1-26	101.3	1319
1-27	19.0	619.8
1-28	7.7	656
1-29	47.6	640.3
1-30	23.9	1508
1-31	18	1138
1-32	6.2	5092
1-33	1.6	270.5
1-34	23.2	5364
1-35	6.9	20537
1-36	1.2	7236
1-37	14.2	1423
1-38	5	75.3
1-39	6.8	1336
1-40	10	1015
1-41	7	954.3

For the compounds of Table 2 the CB1 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 0.35 and 33.1. The CB2 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 127 and 1490. The CB1 cannabinoid receptor selectivity for some of the synthesized analogs range from about 22 to about 480. The cannabinoid receptor binding affinities (Ki) for the synthesized analogs of Table 2 are summarized in Table 7.

Table 7		
Compound no.	CB1 Ki	CB2 Ki
2-1	33.1	1490
2-2	19.7	440.5
2-3	0.35	127

For the compounds of Table 3 the CB1 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 1 and 27. The CB2 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 78 and 750. The CB1 cannabinoid receptor selectivity for some of the synthesized analogs range from about 6 to about 250. The cannabinoid receptor binding affinities (Ki) for the synthesized analogs of Table 5 are summarized in Table 8.

Table 8				
Compound	Receptor Affinities Ki (nM)		Selectivity	
	CB1	CB2	CB1	CB2
3-1	6	265	44	
3-2	16	165	10	
3-3	3	750	250	
3-4	21	313	15	
3-5	2	144	72	
3-6	7	199	28	
3-7	3	116	39	
3-8	12	440	36	
3-9	27	257	9	
3-10	2	279	140	
3-11	1	82	82	
3-12	13	78	6	

For the compounds of Table 4 the CB1 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 2 and 100. The CB2 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 43 and 7,538. The CB1 cannabinoid receptor selectivity for some of the synthesized analogs range from about 3 to about 250. The cannabinoid receptor binding affinities (Ki) for the synthesized analogs of Table 5 are summarized in Table 9.

Table 9				
Compound	Receptor Affinities Ki (nM)		Selectivity	
	CB1	CB2	CB1	CB2
4-1	26	230	8	
4-2	2	43	21	
4-3	31	7538	243	
4-4	13	2294	176	
4-5	3	177	59	
4-6	21	66	3	
4-7	100	290	3	

For the compounds of Table 5 the CB1 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 8 and 87. The CB2 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 13 and 1,527. The CB1 cannabinoid receptor selectivity for some of the synthesized analogs range from about 1 to about 50. The cannabinoid receptor binding affinities (Ki) for the synthesized analogs of Table 5 are summarized in Table 10.

Table 10				
Compound	Receptor Affinities Ki (nM)		Selectivity	
	CB1	CB2	CB1	CB2
5-1	51	76	1.5	
5-2	68	88	1.3	
5-3	30	66	2.2	
5-4	21	40	2	
5-5	30	30	1	
5-6	12	20	1.5	
5-7	20	68	3.5	
5-8	9	13	1.5	
5-9	50	59	1	
5-10	15	54	3.6	
5-11	25	25	1	
5-12	8	421	52	
5-13	20	732	36	
5-14	46	947	20	
5-15	87	1527	17	

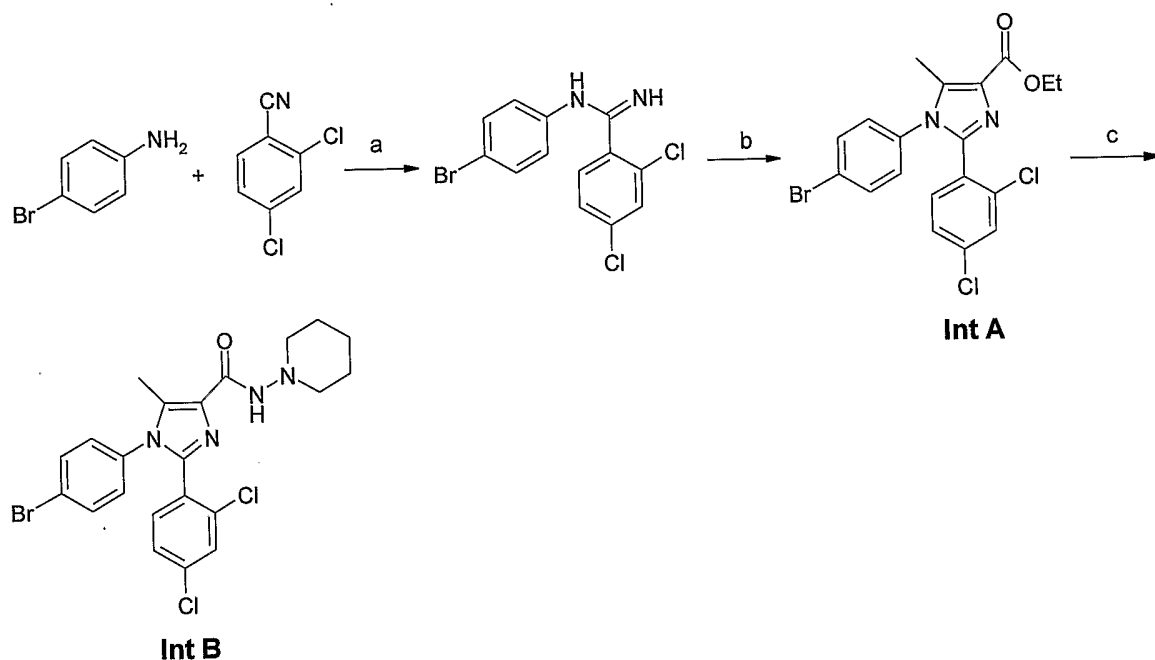
Preparation of compounds

General. Column chromatography was carried out by using Horizon, HPFC system available from Biotage, Inc., Charlottesville, VA. Eluents were distilled before use. Solvents for reactions were dried or purified as required. Reactions were carried out under argon atmosphere unless otherwise noted. All of the reagents are available from Sigma-Aldrich Fine Chemicals of Milwaukee, Wisconsin and/or Lancaster Synthesis Inc. of Windham, New Hampshire.

Modification of the direct aromatic substitution at Imidazole position 1 can be obtained by varying the respective starting aniline (i.e. 4-Bromoaniline).

Modification at imidazole position 2 can be obtained by varying the respective starting material (2,4-dichlorobenzonitrile).

Method A: Modification at Imidazole Positions 1, 2 and 4



(a) EtMgBr, THF; (b) Ethyl-3-bromo-2-oxo butanoate, Na₂CO₃, toluene; (c) 1-aminopiperidine, AlCl₃, 1,2-dichloroethane

2,4-dichloro-N-(4-bromophenyl)benzenecarboxyimidamide.

To a magnetically stirred solution of EtMgBr (3.3 mL, 3M in diethyl ether, 10 mmol) in THF (30 mL) was slowly added 4-bromoaniline portion wise. After the solution was stirred for 30 min., 2,4-dichlorobenzonitrile (1.72g, 10 mmol) was added. The resulting solution was stirred at room temperature (RT) overnight. The reaction mixture was quenched with water and extracted with ethyl acetate.

The combined extracts were dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure.

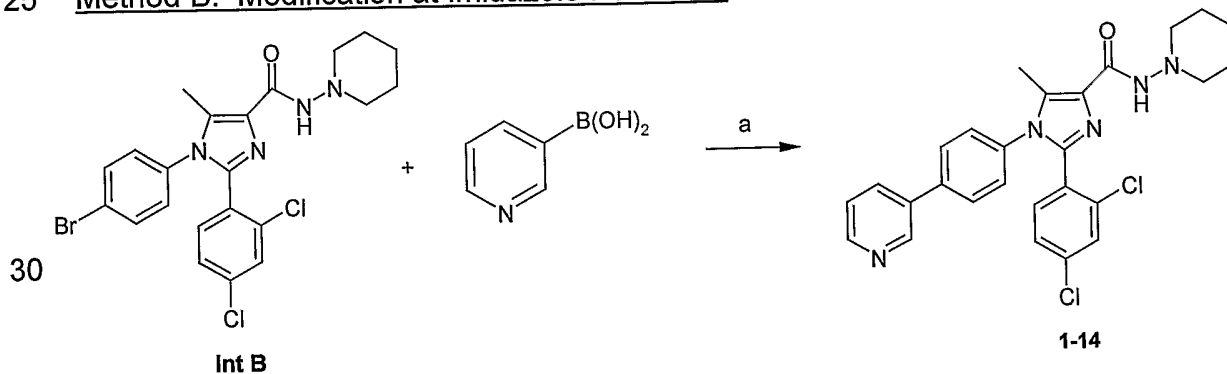
Ethyl 1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxylate (Int A)

To a magnetically stirred solution of above imidamide (2.45g, 7 mmol) in 30 mL anhydrous toluene were added ethyl 3-bromo-2-oxobutanoate (1.48g, 7 mmol) and Na_2CO_3 (0.74g, 7 mmol). The contents were stirred at 100 °C for 12 hours (h). The reaction was brought to RT. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined extracts were dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure. Purification by column chromatography gave the **Int A**.

1-(4-bromophenyl)-2-(2,4-dichlorophenyl)-5-methyl-N-(1-piperidinyl)-1H-imidazole-4-carboxylate (Int B)

To the suspension of AlCl_3 (1.0g, 8 mmol) in dichloroethane (20 mL) was added 1-aminopiperidine (1.2 mL, 12 mmol) at 0 °C and stirred for 25 min at that temperature. To this was added a solution of **Int A** (1.81g, 4 mmol) in dichloroethane (5 mL). The reaction was brought to RT and stirred at that temperature for 8h. The reaction was quenched with dil. HCl and the organic layer was extracted with dichloromethane. The combined extracts were dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure. Purification by column chromatography gave the **Int B**.

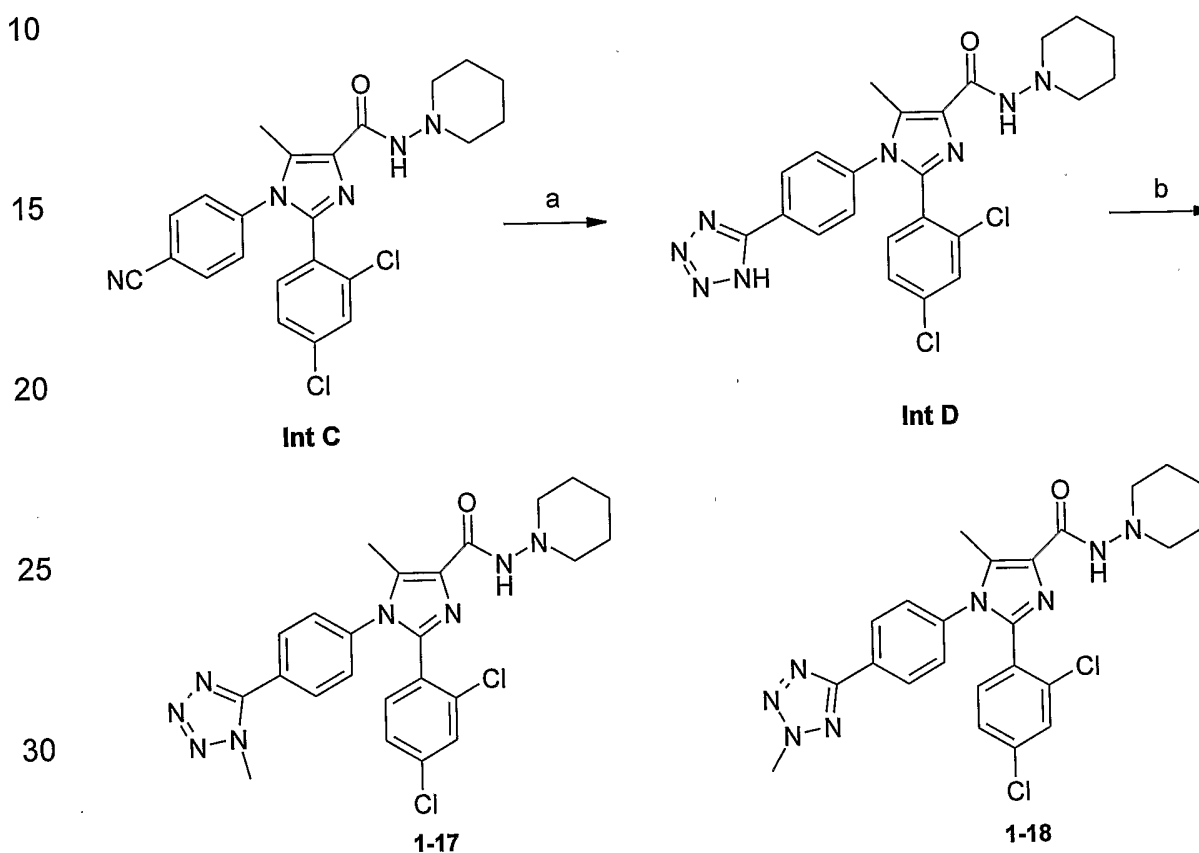
Method B: Modification at Imidazole Position 1



(a) $\text{Pd}(\text{PPh}_3)_4$, $\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$, DME

To the suspension of Pd (PPh₃)₄ (0.046g, 0.04 mmol) in anhydrous DME (10 mL) was added **Int B** (0.2g, 0.4 mmol). The mixture was stirred at RT for 30 min. To this solution were added sequentially the pyridine-3-boronic acid (0.058g, 0.48 mmol), Ba(OH)₂·8H₂O (0.189g, 0.6 mmol) and 0.3mL of water and the mixture was refluxed for 18h., and subjected to filtration. The filtrate was evaporated to dryness. The crude reaction mixture was subjected to column chromatography to yield the biaryl product 1-14.

Method C: Modification at Imidazole Position 1

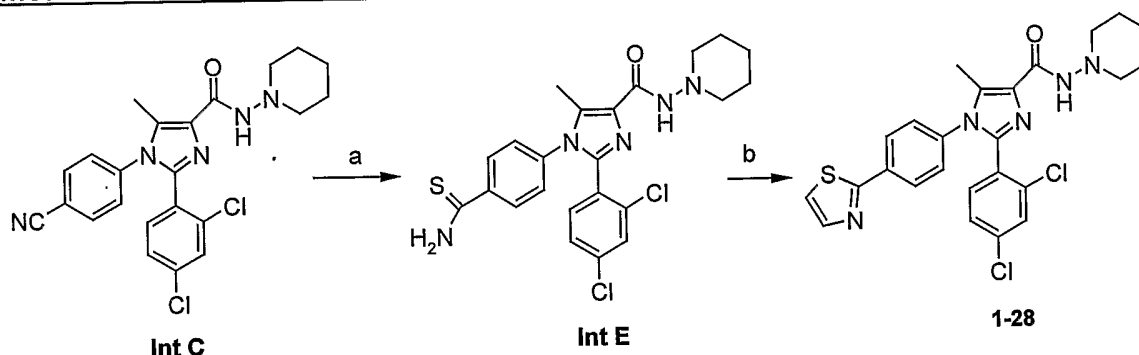


(a) NaN₃, Et₃N·HCl, toluene; (b) CH₃I, K₂CO₃, CH₃CN

Int. D. The mixture of Int I (1.44g, 3.19 mmol), NaN₃ (0.65g, 10 mmol) and Et₃N·HCl (1.37g, 10 mmol) in toluene (25 mL) was heated to 70 °C for 12h with stirring. After cooling, the product was extracted with water. The aqueous layer, 36% HCl was added dropwise to salt out the title product. After filtration, the solid was dried under reduced pressure.

Compounds 1-17 and 1-18. To the **Int D** (0.49g, 1 mmol) in CH₃CN (10 mL) K₂CO₃ (0.13g, 1 mmol) was added. To this CH₃I (0.12 ml, 2 mmol) was added. The contents were stirred at room temperature for 4-5 hrs. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. Two isomers **1-17** and **1-18** were separated and purified by column chromatography.

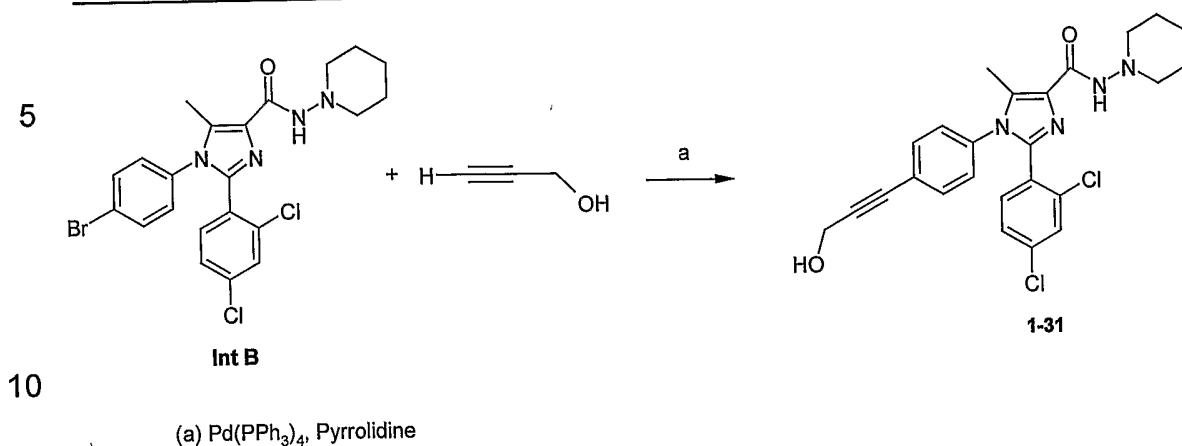
Method D: Modification at Imidazole Position 1



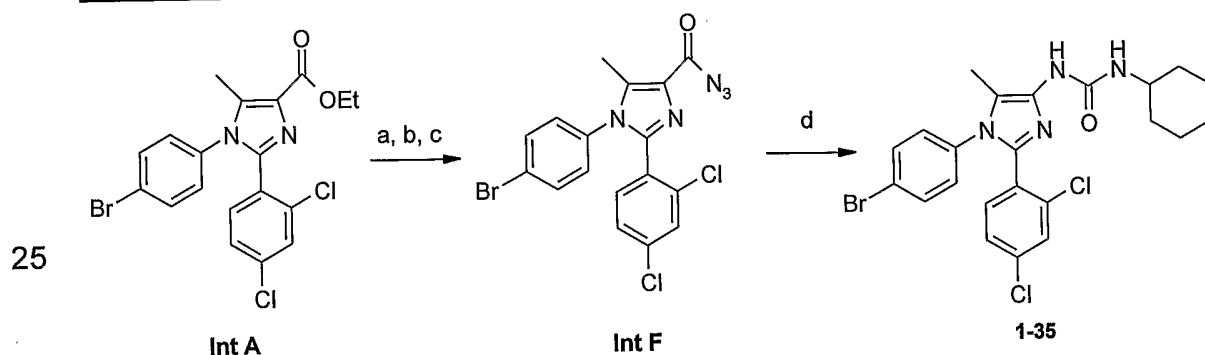
(a) Diethyl dithiophosphate, dioxane/water (b) Bromoacetaldehyde diethylacetal, DMF

Int E: To the **Int C** (0.45g, 1 mmol) in dioxane : water (6:4) (20 mL) diethyl dithiophosphate was added. The contents were stirred at 100 °C for 12h. The reaction was brought to RT and the organic layer was extracted with diethyl ether. The ether layer was washed with NaHCO₃ and dried over anhydrous MgSO₄. The solvent was removed to yield the titled product. See Tetrahedron, 1989, 45, 4599, the contents of which are herein incorporated by reference.

Compound 1-28: To the above **Int E** (0.24g, 0.5 mmol) in DMF (5 mL), bromoacetaldehyde diethylacetal (0.15 mL, 1 mmol) was added and the contents were stirred at 100 °C for 8h. The contents were brought to RT. Water was added and the product was extracted with ethyl acetate. The organic layer was separated and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure to yield the title product.

Method E: Modification at Imidazole Position 1

To a stirred solution of Int B (0.5g, 1 mmol) in pyrrolidine (15 mL), propargyl alcohol (0.05g, 1mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.11g, 0.1 mmol) were added. The contents were stirred at 90 °C for 12h. After cooling the reaction mixture to RT, water (50 mL) was added. The product was extracted with ethyl acetate. The organic layer was dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure. Purification by column chromatography gave the product **1-31**.

Method F: Modification at Imidazole Position 4

(a) LiOH , $\text{THF}/\text{MeOH}/\text{H}_2\text{O}$; (b) SOCl_2 , toluene; (c) aq. NaN_3 , THF ; (d) cyclohexylamine, toluene;

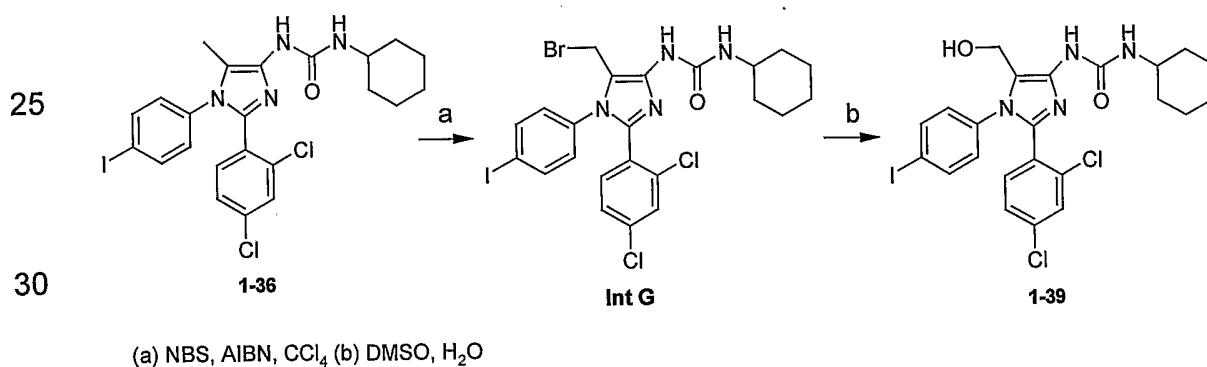
Int. F. To a magnetically stirred solution of ester Int. A (0.626 g, 1.38 mmol) in THF : methanol: water (7:2:1, 15 mL) lithium hydroxide monohydrate (0.08 g, 2 mmol) was added. The mixture was heated under reflux for 3 h. The cooling reaction mixture was then poured into water (10 mL) and acidified with 10%

hydrochloric acid. The precipitate was filtered, washed with water, and dried under vacuum to yield the corresponding acid as a solid.

A solution of the crude acid (0.585 g) and thionyl chloride (0.492 g, 4.14 mmol) in toluene (10 mL) was refluxed for 3 h. Solvent was evaporated under reduced pressure, and the residue was then redissolved in toluene (20 mL) and evaporated to yield the crude carboxylic chloride as a solid. To the solution of above carboxylic chloride (1.24 mmol) in THF (5 mL), NaN₃ (0.081g, 1.24 mmol) in 0.5 mL of water was added at 0 °C. The contents were stirred at that temperature for 1 hr. The reaction was quenched with water (5 mL), both aqueous and organic layers were separated. The organic layer was extracted using ethyl acetate (10 mL) and dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure to give the title product.

Compound 1-35. To a magnetically stirred solution of Int. F (0.448 g, 1 mmol) in toluene (10 mL) cyclohexyl amine (0.34 mL, 3 mmol) was added. The contents were stirred at 100 °C for 8h. After cooling to room temperature the reaction was quenched by water (5 mL). Both aqueous and organic layers were separated, the organic layer was dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure. Purification by column chromatography gave the title product.

Method G: Modification at Imidazole Position 5



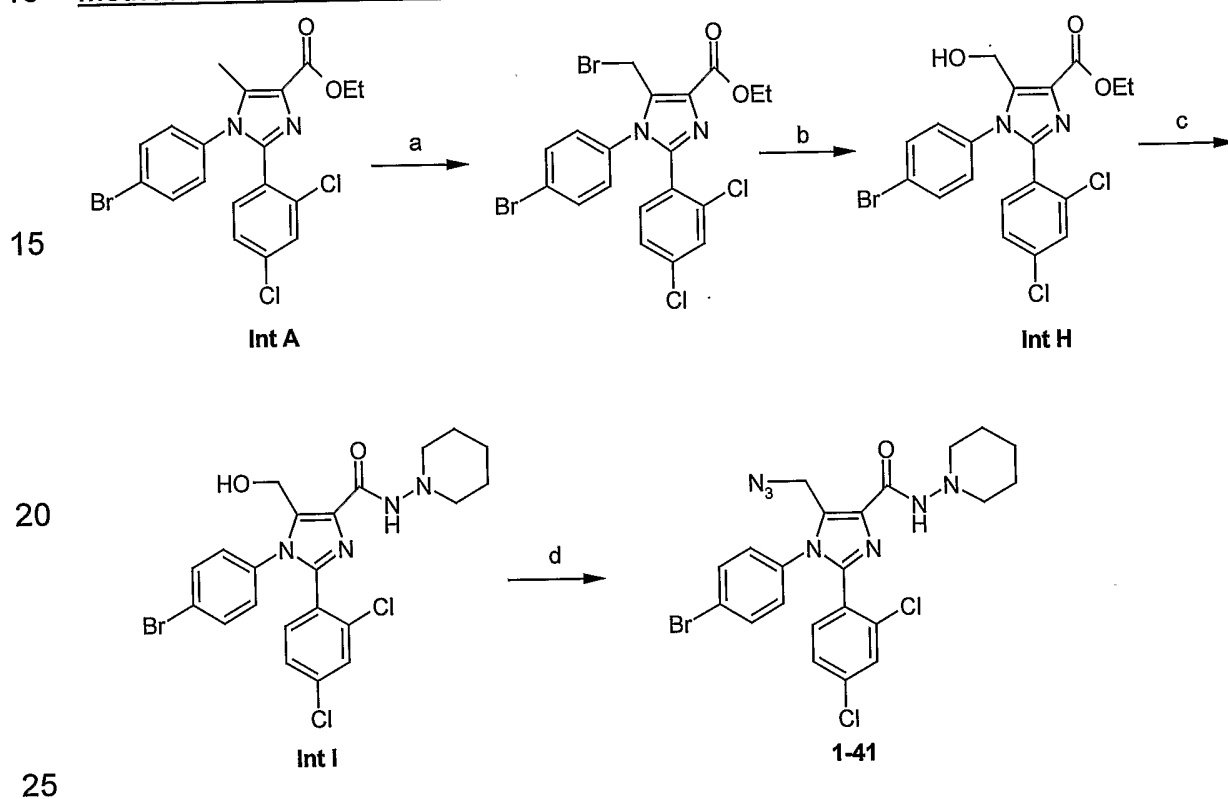
Int. G. To a magnetically stirred solution of **1-36** (0.569g, 1 mmol) in carbon tetrachloride (20 mL) was added *N*-bromosuccinimide (0.21g, 1.2 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 5 mg). The resulting mixture was refluxed for 3 h.

After cooling to RT, the precipitate was filtered. The solvent was removed from the filtrate under reduced pressure to give the title product.

Compound 1-39. To the Int. G (0.648g, 1 mmol), DMSO/H₂O (5:1) were added.

- 5 The mixture was stirred at 60 °C for 5h. After cooling to RT, water (30 mL) was added. The organic layer was extracted with ethyl acetate and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. Purification by column chromatography gave the title product.

10 Method H: Modification at Imidazole Position 5



(a) NBS, AIBN, CCl₄; (b) DMSO/H₂O; (c) 1-aminopiperidine, AlCl₃, 1,2-dichloroethane
(d) Diphenylphosphoryl azide, DBU, toluene

- 30 **Int H** To a magnetically stirred solution of Int A (0.454g, 1 mmol) in carbon tetrachloride (20 mL) was added *N*-bromosuccinimide (0.21g, 1.2 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 5 mg). The resulting mixture was refluxed for 3 h. After cooling to RT, the precipitate was filtered. The solvent was removed from the filtrate under reduced pressure gave the bromo derivative, to which DMSO/H₂O (5:1) were added. The mixture was stirred at 60 °C for 5h. After

cooling to RT, water (30 mL) was added. The organic layer was extracted with ethyl acetate and dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure. Purification by column chromatography gave the title product.

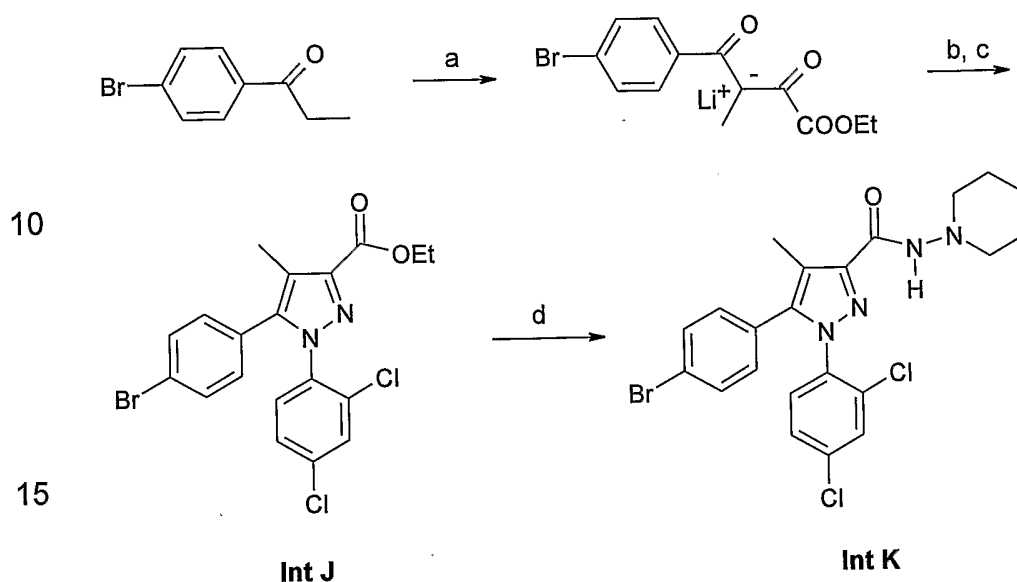
- 5 **Int I** To the suspension of AlCl_3 (0.266g, 2 mmol) in dichloroethane (20 mL) was added 1-aminopiperidine (0.6 mL, 6 mmol) at 0 °C and stirred for 25 min at that temperature. To this was added a solution of Int H (0.94g, 2 mmol) in dichloroethane (5 mL). The reaction was brought to RT and stirred at that temperature for 8h. The reaction was quenched with dil. HCl and the organic
10 layer was extracted with dichloromethane. The combined extracts were dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure. Purification by column chromatography gave the Int I.

- Compound 1-41** A mixture of Int I (0.52g, 1 mmol) and diphenyl phosphorazidate
15 (DPPA) (0.25 mL, 1.2 mmol) was dissolved in anhydrous toluene (10 mL). The mixture was cooled to 0 °C under argon, and neat DBU (0.18 mL, 1.2 mmol) was added. The reaction was stirred for 2h at 0 °C and then at RT for 16h. The resulting two-phase mixture was washed with water and 5% HCl. The organic layer was extracted with ethyl acetate and dried over anhydrous MgSO_4 . The
20 solvent was removed under reduced pressure. Purification by column chromatography gave the product **1-41**. See J. Org. Chem., 1993, 58, 5886, the contents of which are herein incorporated by reference.

PROPHETIC METHODS

Methods I-L are prophetic and are believed useful to prepare the inventive compounds of formulas II and III.

5 Method I: Modification at Pyrazole Positions 1, 3 and 5



(a) LiHMDS, ether, then EtO₂CCO₂Et; (b) 2, 4-Dichlorophenylhydrazine hydrochloride, EtOH; (c) AcOH; (d) 1-Aminopiperidine, AlCl₃, 1,2 dichloroethane.

Lithium salt of ethyl 2,4-dioxo-3-methyl-4-(4-bromophenyl)butanoate.

To a magnetically stirred solution of lithium bis(trimethylsilyl)amide (40 mL, 1.0 M solution in hexane, 40 mmol) in diethyl ether (120 mL) was added a solution of 4'-bromopropiophenone (8.52 g, 40 mmol) in diethyl ether (50 mL) at -78 °C.

25 After the mixture was stirred at the same temperature for an additional 45 min, diethyl oxalate (6.4 mL, 47 mmol) was added to the mixture. The reaction mixture was allowed to warm to room temperature (RT) and stirred for 16 h. The precipitate was filtered, washed with diethyl ether, and dried under vacuum to afford the lithium salt.

1-(2,4-Dichlorophenyl)-4-methyl-5-(4-bromophenyl)-1H-pyrazole-3-carboxylic acid, Ethyl Ester (Int. J).

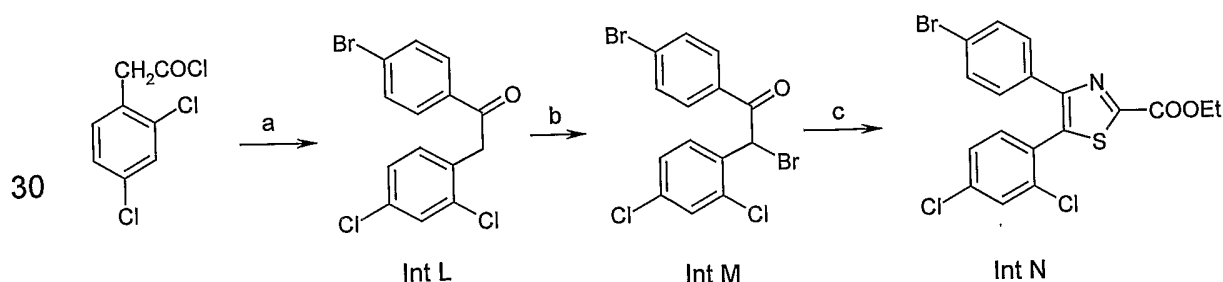
To a magnetically stirred solution of the above lithium salt (0.64g, 2.0 mmol) in 10 mL of ethanol was added 2,4-dichlorophenylhydrazine hydrochloride (0.47g, 2.2 mmol) at room temperature. The resulting mixture was stirred at room temperature for 20 h. The precipitate was filtered, washed with ethanol and diethyl ether, and then dried under vacuum to give a light yellow solid. This solid was dissolved in acetic acid (7 mL) and heated under reflux for 24 h. The reaction mixture was poured into cold water and extracted multiple times with ethyl acetate. The combined extracts were washed with water, saturated aqueous sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash column chromatography on silica gel gave the expected ester Int. J

15 N-(Piperidin-1-yl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (Int. K).

To the suspension of AlCl_3 (1.0g, 8 mmol) in dichloroethane (20 mL) was added 1-aminopiperidine (1.2 mL, 12 mmol) at 0 °C and stirred for 25 min at that temperature. To this was added a solution of **Int J** (1.81g, 4 mmol) in dichloroethane (5 mL). The reaction was brought to RT and stirred at that temperature for 8h. The reaction was quenched with dilute HCl and the organic layer was extracted with dichloromethane. The combined extracts were dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure. Purification by column chromatography gave the **Int K**.

25

Method J: Modification at Thiazole Positions 2, 4 and 5



(a) AlCl_3 , bromobenzene; (b) Br_2 , CHCl_3 ; (C) ethyl thiooxamate, Ethanol

2-(2,4-dichlorophenyl)-1-(4-bromophenyl)ethanone (Int L)

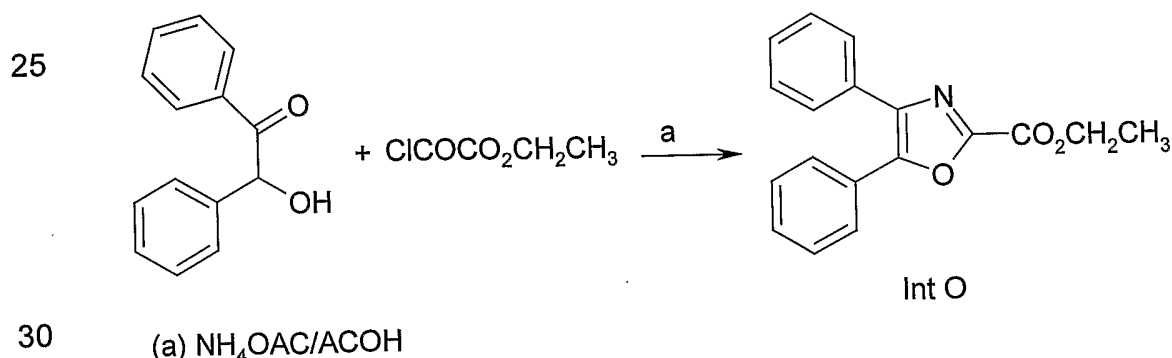
To the solution of 2,4-dichlorobenzyl chloride (2.33g, 10 mmol) in bromobenzene at 0°C, AlCl₃ (1.72g, 13 mmol) will be slowly added. The reaction mixture will be stirred overnight at room temperature. The reaction will be poured onto ice and extracted with ethyl acetate. The combined organic layers will be evaporated to yield the title compound.

2-Bromo-1-(4-bromophenyl)-2-(2,4-dichlorophenyl)ethanone (Int M)

To the stirring solution of Int L (3.44g, 10 mmol) in chloroform (40 mL) bromine (1 mL, 15 mmol) will be added slowly. The contents will be stirred at 65-70 °C for 4h. The reaction mixture will be brought to room temperature. Water will be added and the organic layer will be separated and dried over anhydrous MgSO₄. The evaporation of solvent will result in int M.

Ethyl-5-(2,4-dichlorophenyl)-4-(4-bromophenyl)thiazole-2-carboxylate (Int N)

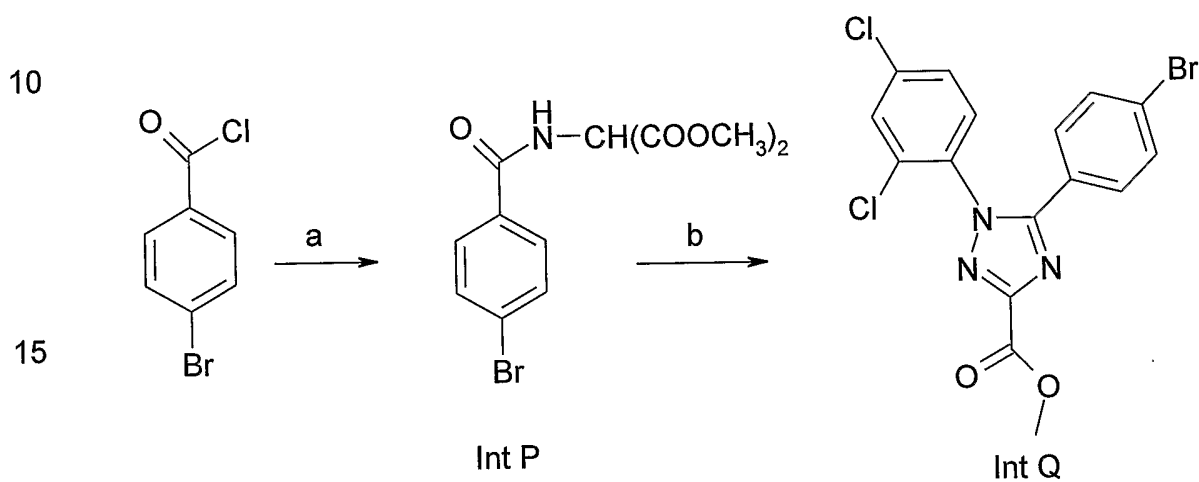
Int M (4.2 g, 10 mmol) and ethyl thiooxamate (1.9g, 15 mmol) will be dissolved in ethanol. The resulting solution will be heated at reflux temperature for 4-5h. The reaction will be brought to room temperature and the solvent will be evaporated. The resulting crude will be purified by column chromatography to yield the title compound.

Method K: Modification at Oxazole Positions 2, 4 and 5**Ethyl 4,5-diphenyl-2-oxazolecarboxylate (Int O)**

Ethyl oxalyl chloride (1.1 mL, 10 mmol) will be added dropwise to a stirring solution of 2-hydroxy-1,2-diphenyl ethanone (2.12g, 10 mmol) and triethyl amine

(2.2 mL, 16 mmol) in anhydrous THF (50 mL) under argon. After stirring for 45 min the mixture will be filtered and concentrated, and NH_4OAc (4g, 50 mmol) and acetic acid (50 mL) will be added. The mixture will be heated to reflux for 6h. The reaction will be brought to room temperature and water will be added and
 5 extracted with dichloromethane and the residue will be subjected to column chromatography to yield the title compound.

Method L: Modification at Triazole Positions 1,3 and 5



(a) dimethyl aminomalonate hydrochloride, Et_3N , CH_2Cl_2 ;
 20 (b) 2,4-dichloroaniline, aq. HCl, AcOH, NaNO_2 , NaOMe, Methanol

Dimethyl-2-(4-bromobenzoylamino)malonate (Int P)

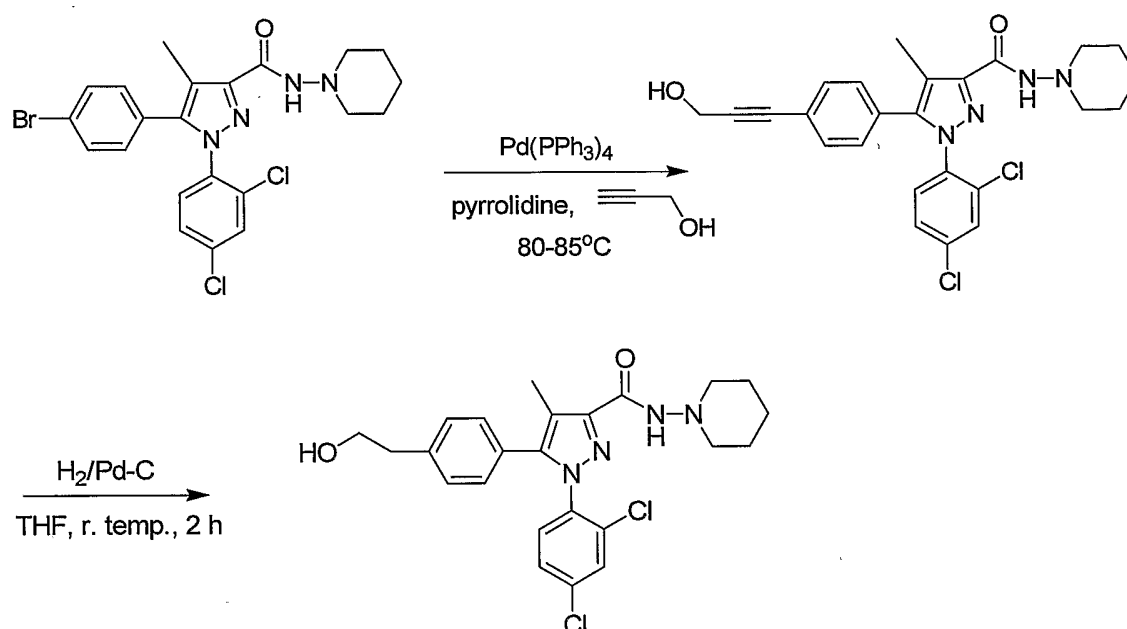
To a stirred solution of dimethyl aminomalonate hydrochloride (1.83g, 10mmol) in dichloromethane (30 mL) triethylamine (3 mL, 22 mmol) will be added
 25 at 0°C . 4-bromobenzoyl chloride (2.19g, 10 mmol) will be slowly added the resulting solution will be allowed to stand at room temperature overnight. Water will be added and the organic layer will be separated and dried over anhydrous MgSO_4 . The evaporation of solvent will result in Int P.

30 **Methyl 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-1H-1,2,4-triazole-3-carboxylate (Int Q)**

To a stirred solution of 2,4-dichloroaniline (1.62 g, 10 mmol) in conc. HCl (5 mL) and acetic acid (30 mL) at 0°C will be added a solution of NaNO_2 (0.69g, 10 mmol) in water (10 mL) and resulting solution will be stirred for 15 min. A

solution of Int P (2.37g, 8.3 mmol) in acetone (20 mL) will be slowly added while keeping the temperature below 0°C. A solution of K₂CO₃ (1.2g) in water (20 mL) will be slowly added and the resulting mixture will be stirred for 30 min at 0°C. The resulting mixture will be extracted with ethyl acetate. The organic layer will be washed with water and NaHCO₃ and dried over anhydrous MgSO₄. The solvent will be evaporated and dissolved in methanol and NaOMe will be added. The resulting mixture will be allowed stand overnight at room temperature and cooled in refrigerator. The title compound will precipitate out.

10 Method M: Modification at Pyrazole Positions 3 and 5



15 **1-(2, 4-Dichloro-phenyl)-5-[4-(3-hydroxy-prop-1-ynyl)-phenyl]-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide (2-1)**

To a stirred solution of 5-(4-Bromo-phenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide (40 mg, 0.078 mmol) in pyrrolidine (2.5 ml) was added a catalytic amount of tetrakis (triphenylphosphine) palladium under an atmosphere of Argon. After stirring the contents for 5 min at room temperature, a solution of propargyl alcohol (10 mg, 0.178m mol) in pyrrolidine (1.5 ml) was added to the reaction mixture. The contents were heated at 80-85 °C for 10 h. Then a saturated aqueous solution of ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic extract

was dried over MgSO_4 and the solvent was removed in vacuo. Purification by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 7: 3) afforded 28 mg (74 %) of **2-1** as white solid.

5 **1-(2, 4-Dichloro-phenyl)-5-[4-(3-hydroxy-propyl)-phenyl]-4-methyl-1H-pyrazole-3-carboxylic acid piperidin-1-ylamide (4-1)**

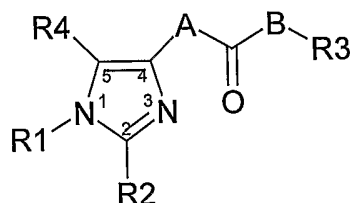
To a magnetically stirred suspension of 14 mg of palladium (10 wt % on carbon) taken in 8 ml of THF was added compound **2-1** (80 mg, 0.165 mmol) dissolved in 3ml of THF. The resulting mixture was stirred at room temperature
10 for 2 h under an atmosphere of hydrogen. Then to the mixture was added 10 ml of DCM and the catalyst was filtered and the residue was concentrated and purified by flash column chromatography (petroleum ether- ethyl acetate, 6: 4) to afford 61 mg (76 %) of **4-1** as a white solid.

Compounds **3-1** to **3-12** as shown in Table 3 and compounds **4-2** to **4-7** as
15 shown in Table 4 were synthesized according to the above represented examples. Similarly compounds **5-1** to **5-21** shown in Table 5 were synthesized using other commercially available acetylenes.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to specific embodiments of the
20 invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the invention.

What is claimed is:

1. A compound represented by the following structural formula,



and physiologically acceptable salts thereof, wherein:

A is selected from a direct bond, O and $-(CH_2)_lN(R_5)$;

B is selected from a direct bond, O and $N(R_5)$,

R5 is selected from hydrogen, alkyl and substituted alkyl and l is 0 or

1;

R1 and R2 are each independently $-(CH_2)_n-Z$,

n is an integer from 0 to about 7, and

Z is selected from H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, C(halogen)₃, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X_1 and X_2 are each independently selected from H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ,

j is an integer from 0 to about 6; or

Z is selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic

ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

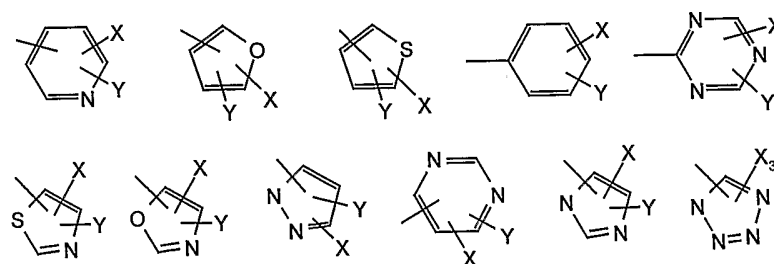
Z is selected from a 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a substituted 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a 6 member aromatic ring having 0 to 5 independently selected heteroatoms as ring members or a substituted 6 member aromatic ring having 0 to 5 independently selected heteroatoms; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

R1 and R2 are each independently $-(CH_2)_n-Z$,

n is an integer from 0 to about 7, and

Z is selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from



wherein X and Y are each independently selected from H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aryl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aryl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl and methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X₁ and X₂ are each independently selected from H and alkyl, or

X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members,

X₃ is selected from H, alkyl, hydroxyloweralkyl and alkyl-NX₁X₂; or

Z is selected from a carbocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a carbocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an heterocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heteroaromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms or a heteroaromatic ring

having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms; or

Z is selected from an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 3 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 4 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members; or

R1 and R2 are each independently $-Q_2-(CH_2)_n-Z$,

Q_2 is optionally present and if present is selected from $-CH_2-N$, $-CH_2-O$, $-CH_2-S$, $-CH_2-SO_2$ and $-CH_2-OSO_2$,

n is an integer from 0 to about 7, and

Z is selected from H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aroyl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aroyl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X_1 and X_2 are each independently selected from H and alkyl,

or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ,

j is an integer from 0 to about 6; or

R1 and R2 are each independently $-(CH_2)_m-Q_1-(CH_2)_n-Z$,

Q_1 is selected from N, O, S, $-CH=CH-$, $-C\equiv C-$, $-CO$, SO_2 and OSO_2 ,

m is an integer from 1 to about 7,

n is an integer from 0 to about 7, and

Z is selected from H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOH$, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X_1 and X_2 are each independently selected from H and alkyl,

or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ,

j is an integer from 0 to about 6; or

Z is selected from a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring and a heteropolycyclic ring; or

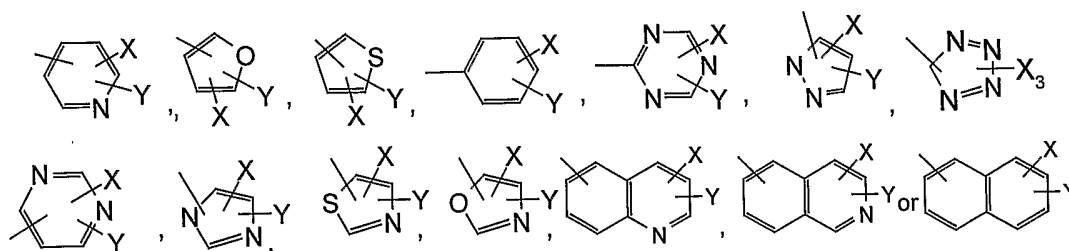
Z is selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members; a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring or any above group substituted on at least one available ring atom by an alkyl group or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the

connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from a 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a substituted 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a 6 member aromatic ring having 0 to 5 independently selected heteroatoms as ring members or a substituted 6 member aromatic ring having 0 to 5 independently selected heteroatoms; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from



wherein X and Y are each independently selected from H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, C(halogen) $_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy,

alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl and methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 are each independently selected from H and alkyl, or

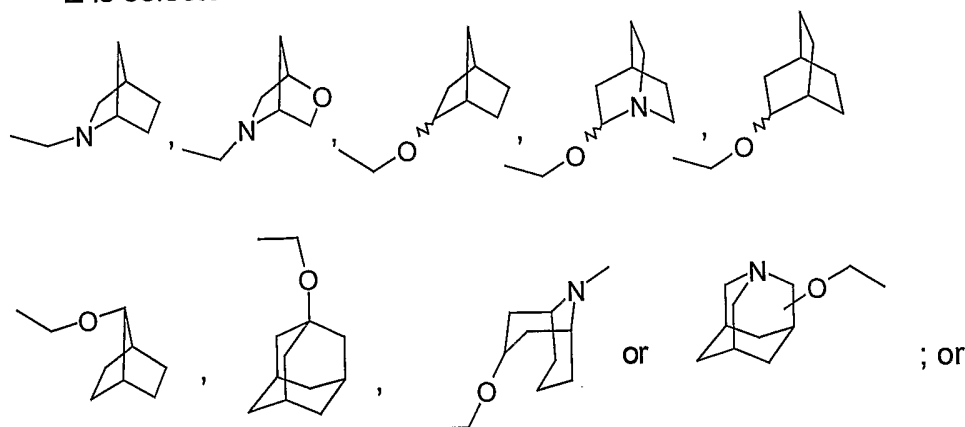
X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ; or

Z is selected from an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 4 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members; or

Z is selected from



R1 and R2 are each independently $-T-(CH_2)_n-Z$,

n is an integer from 0 to about 7,

T is selected from a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring and a heteropolycyclic ring, and

Z is selected from H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOH$, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X_1 and X_2 each independently is selected from H and alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and or alkyl- NX_1X_2 ,

j is an integer from 0 to about 6; or

Z is selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

R1 and R2 are each independently $-T-(CH_2)_n-Q_1-(CH_2)_n-Z$,

each n is independently an integer from 0 to about 7,

T is selected from a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring and a heteropolycyclic ring,

Q_1 is selected from N, O, S, CH=CH, C≡C, CO, SO₂ and OSO₂, and

Z is selected from H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aroyl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aroyl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X_1 and X_2 each independently selected from H and alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl-NX₁X₂,

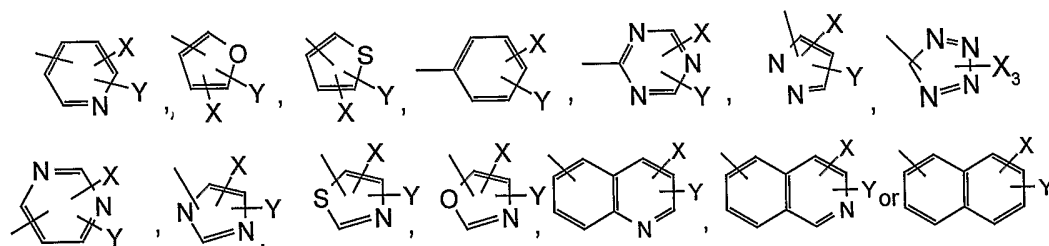
j is an integer from 0 to about 6; or

Z is selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted

benzhydryl group; and wherein the connecting point between the $-(CH_2)_n$ - group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n$ - group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from



wherein X and Y are each independently is selected from H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, C(halogen) $_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl and methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 are each independently is selected from H and alkyl, or

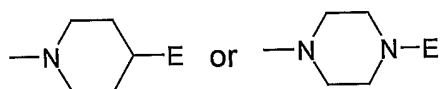
X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ; or

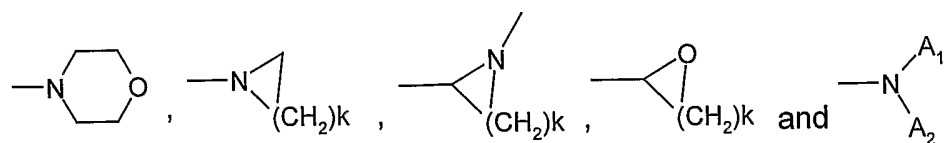
Z is selected from an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 3 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members; or

Z is selected from



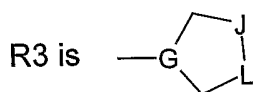
wherein E is selected from a C1 to about C4 linear or branched alkyl group, a phenyl group, a substituted phenyl group, a benzyl group and a substituted benzyl group; or

Z is selected from

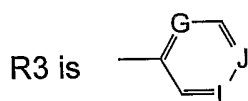


wherein k is an integer from 1 to about 5, A₁ and A₂ are each independently selected from a C1 to about C4 alkyl group, a phenyl group and a substituted phenyl group;

R3 is selected from a carbocyclic ring having about 4 to about 7 members, a heterocyclic ring having about 4 to about 7 members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring and a heteropolycyclic ring; or

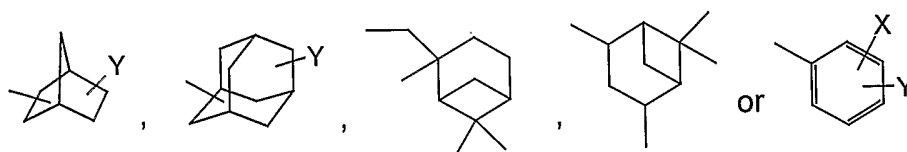


wherein G is selected from CH and N, and L and J each independently selected from (CH₂)_n, O, NH and S, n is an integer from 0 to about 7; or



wherein G, L and J are each independently selected from CH and N;
or

R3 is selected from



wherein X and Y are independently selected from H, halogen, N₃, NCS, phenyl, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aroyl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aroyl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X₁ and X₂ are each independently selected from H and alkyl,

or

X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members),

X₃ is selected from H, alkyl, hydroxyloweralkyl and alkyl-NX₁X₂,

j is an integer from 0 to about 6; or

R₃ is selected from a carbocyclic ring having 4 to 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a carbocyclic ring having 4 to 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heteroaromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, and a heteroaromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms;

R₄ is selected from H, halogen, N₃, NCS, phenyl, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aroyl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aroyl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X₁ and X₂ are each independently selected from H and alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

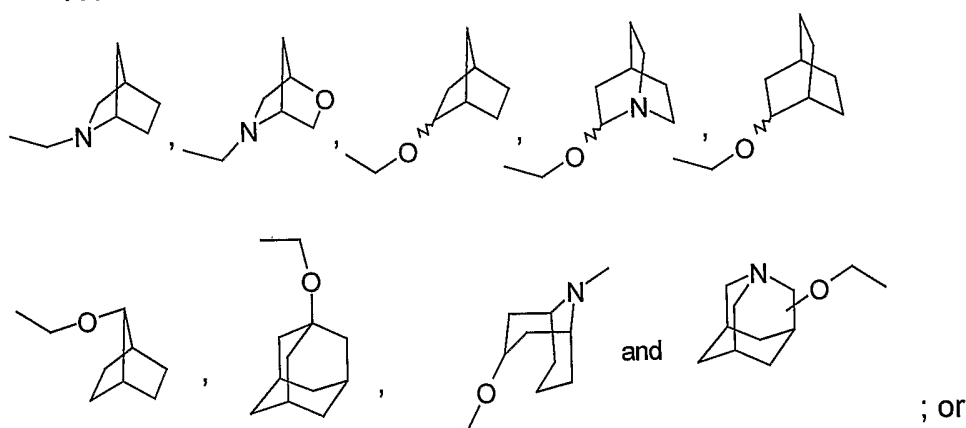
X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members),

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ,

j is an integer from 0 to about 6; or

R_4 is selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring and a heteropolycyclic ring; or

R_4 is selected from



R_4 is $-(CH_2)_d-Z$,

d is an integer from 1 to about 6, and

Z is selected from H, halogen, N_3 , NCS, phenyl, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOH$, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X_1 and X_2 are each independently selected from H and alkyl,
or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members),

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ,

j is an integer from 0 to about 6; or

Z is selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_d-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_d-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

R4 is $-(CH_2)_m-Q_1-(CH_2)_n-Z$,

Q_1 is selected from N, O, S, CH=CH, C≡C, CO, SO₂ and OSO₂,

m is an integer from 1 to about 7,

n is an integer from 0 to about 7, and

Z is selected from H, halogen, N₃, NCS, phenyl, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aryyl, NH-acyl, NH-aryyl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl and alkylsulfonyl,

X_1 and X_2 are each independently selected from H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl-NX₁X₂,

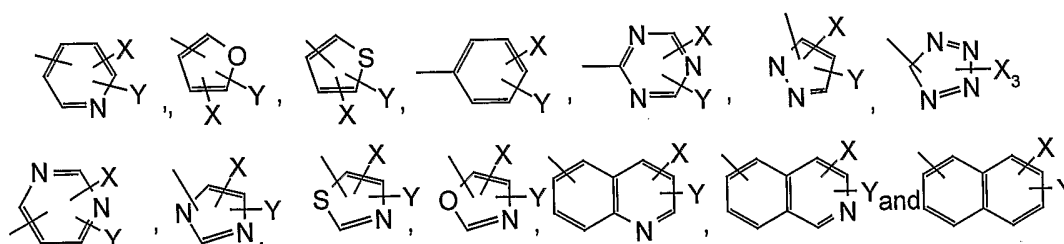
j is an integer from 0 to about 6; or

Z is selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members; a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidyl, 1- or

2-piperaziny, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from



wherein X and Y are each independently selected from H, halogen, N₃, NCS, CN, NO₂, NX₁X₂, OX₃, OAc, O-acyl, O-aroyl, O(CH₂)_jOX₃, O(CH₂)_jNX₁X₂, NH-acyl, NH-aroyl, CHO, C(halogen)₃, COOX₃, SO₃H, SO₂NX₁X₂, CONX₁X₂, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl and methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X₁ and X₂ are each independently selected from H and alkyl, or

X₁ and X₂ together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X₁ and X₂ together comprise part of an imide ring having about 5 to about 6 members,

X₃ is selected from H, alkyl, hydroxyloweralkyl and alkyl-NX₁X₂,

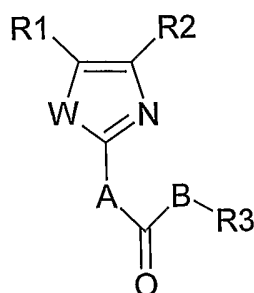
J is an integer from 0 to about 6;

with the proviso that when A is a direct bond; and B is N(R5); and either of R1 and R2 is phenyl [optionally substituted with one more members selected from halogen, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, cyano, nitro, (C₁-C₆) alkyl sulfonyl, (C₁-C₆) alkyl sulfonyl amino, (C₁-C₆) alkyl carbonyl-amino, (C₁-C₆) alkyl amino-carbonyl-amino and phenyl], (C₂-C₆) alkyl, cyclohexyl [optionally substituted with (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, cyano or one or more fluorine atoms], 1-naphthyl or 2-naphthyl [optionally substituted with one or more members selected from halogen, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl and cyano], benzyl [optionally substituted on the phenyl ring with one or more members selected from halogen, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl and cyano], a 5- to 10-membered saturated or unsaturated heterocyclic radical [optionally substituted with one or more members selected from fluorine, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl and cyano] and a 5- to 10- membered aromatic monocyclic or bicyclic heterocyclic radical [optionally substituted with one more members selected from halogen, (C₁-C₆) alkyl, (C₁-C₆) alkoxy, trifluoromethyl, cyano, nitro and phenyl]; then R4 can not be H, (C₁-C₆) alkyl, benzyl, chloro, or bromo;

and the proviso that when A is a direct bond; B is N(R5); and either R1 or R2 is phenyl, thienyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl or any above group substituted with 1, 2, 3 or 4 substituents which can be the same or different, selected from C₁₋₃ alkyl, C₁₋₃ alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkoxycarbonyl, carboxyl, cyano, carbonyl, acetyl and naphthyl; then R4 can not be H, halogen, CN, carbonyl, formyl, acetyl, trifluoroacetyl, fluoroacetyl, propionyl, sulfamoyl, methanesulfonyl, methylsulfonyl, branched or unbranched C₁₋₄ alkyl group, which C₁₋₄ alkyl group may be substituted with 1 to 3 fluoro atoms or with a single bromo, chloro, iodo, cyano or hydroxy group.

2. The compound of claim 1 wherein R4 is selected from -CH₂OH and -CH₂Oalkyl.

3. A compound represented by the following structural formula



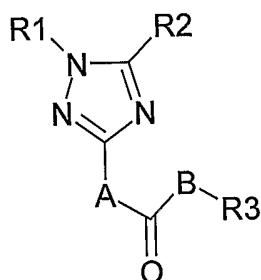
and physiologically acceptable salts thereof, wherein:

A, B, R1, R2 and R3 are as defined in claim 1;

W is selected from S and O;

with the proviso that when A is a direct bond; B is NR₅ as defined in claim 1; R1 and R3 are as defined in claim 1; and W is S; then R2 cannot be a phenyl group with one or more substituents selected from branched or unbranched C₁₋₃-alkyl, branched or unbranched C₁₋₃-alkoxy, hydroxy, halogen, CF₃, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono-or dialkyl(C₁₋₂)-amino, mono-or dialkyl(C₁₋₂)-amido, branched or unbranched (C₁₋₃)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfamoyl, branched or unbranched (C₁₋₃)-sulfonyl, carboxyl, cyano, carbamoyl, branched or unbranched dialkyl(C₁₋₃)-aminosulfonyl, branched or unbranched monoalkyl(C₁₋₃)-aminosulfonyl and acetyl.

4. A compound represented by the following structural formula

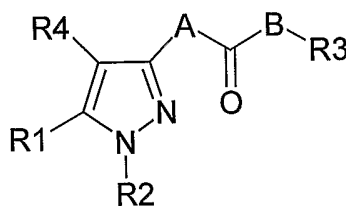


and physiologically acceptable salts thereof, wherein:

A, B, R1, R2 and R3 are as defined in claim 1;

with the proviso that when A is a direct bond; B is NR₅; R3 is as defined in claim 1; then either or both of R1 and R2 cannot be a phenyl, naphthyl, thienyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, or triazinyl group, or any above group substituted with 1-4 substituents, which can be same or different, selected from branched or unbranched (C₁₋₃)alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C₁₋₂)-amino, mono- or dialkyl (C₁₋₂)-amido, (C₁₋₃)-alkoxycarbonyl, trifluoromethylsulfonyl, sulfomyl, (C₁₋₃)-alkylsulfonyl, carboxyl, cyano, carbonyl, (C₁₋₃)-dialkylaminosulfonyl, (C₁₋₃)-monoalkylamino-sulfonyl and acetyl.

5. A compound represented by the following structural formula



and physiologically acceptable salts thereof, wherein:

A, B, R2, R3 and R4 are as defined in claim 1;

R1 is $-T-(CH_2)_n-Q-(CH_2)_n-Z$,

each n is independently an integer from 0 to about 7,

T is selected from a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, an aromatic ring having 5 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring,

Q is optionally present and if present is selected from $CH=CH$ and $C\equiv C$, and

Z is selected from H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aroyl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aroyl, $NHC(O)-O-X_3$, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, SX_1 , $Si(X_1)_3$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl,

X_1 and X_2 are each independently selected from H and alkyl,

or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ,

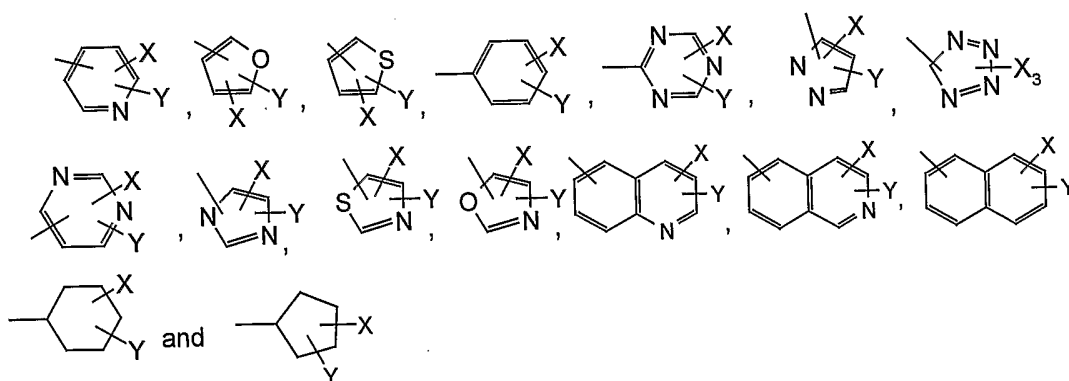
each j is independently an integer from 0 to about 6; or

Z is selected from a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a

heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidiny, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom; or

Z is selected from



wherein X and Y are each independently selected from H, halogen, N_3 , NCS, CN, NO_2 , NX_1X_2 , OX_3 , OAc, O-acyl, O-aryl, $O(CH_2)_jOX_3$, $O(CH_2)_jNX_1X_2$, NH-acyl, NH-aryl, CHO, $C(halogen)_3$, $COOX_3$, SO_3H , $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl and methylene dioxy when Z comprises a structure having two adjacent carbon atoms,

X_1 and X_2 are each independently selected from H and alkyl, or

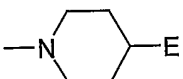
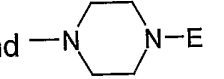
X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X_2 together comprise part of an imide ring having about 5 to about 6 members,

X_3 is selected from H, alkyl, hydroxyloweralkyl and alkyl- NX_1X_2 ,

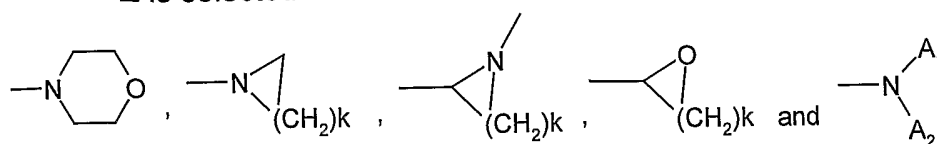
j is an integer from 0 to about 6; or

Z is selected from an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 3 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 4 independently selected heteroatoms as ring members; or

Z is selected from  and ,

E is selected from a C1 to about C4 linear or branched alkyl group, a phenyl group, a substituted phenyl group, a benzyl group and a substituted benzyl group; or

Z is selected from



wherein k is an integer from 1 to about 5, A_1 and A_2 are each independently selected from a C1 to about C4 alkyl group, a phenyl group and a substituted phenyl group.

6. A pharmaceutical composition containing a therapeutically effective amount of at least one of the compounds of claims 1 or 3 through 5.
7. A method of stimulating cannabinoid receptors in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of at least one of the compounds of claims 1 or 3 through 5.
8. A method of selectively stimulating a CB1 cannabinoid receptor in an individual or animal without stimulating a CB2 cannabinoid receptor in that individual or animal to the same degree comprising administering to the individual or animal a therapeutically effective amount of at least one of the compounds of claims 1 or 3 through 5.
9. A method of treating an individual or animal comprising administering to the individual or animal a therapeutically effective amount of at least one of the compounds of claims 1 or 3 through 5.
10. A method of providing a physiological response in an individual or animal comprising administering to the individual or animal a therapeutically effective amount of at least one of the compounds of claims 1 or 3 through 5.