TETRAHYDRO-INDAZOLE CANNABINOID MODULATORS

CROSS REFERENCE TO RELATED APPLICATIONS

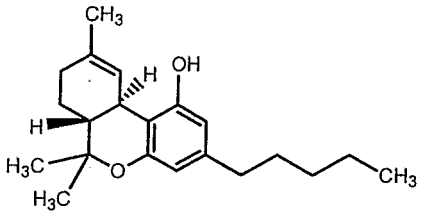
This present application claims benefit of U.S. Provisional Patent Application Serial No. 60/555890, filed March 24, 2004, which is incorporated herein by reference in its entirety and for all purposes.

FIELD OF THE INVENTION

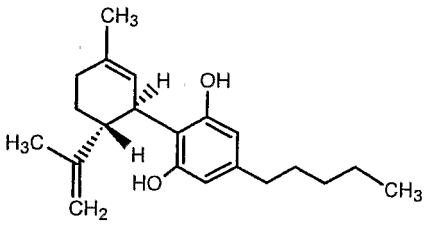
This invention is directed to tetrahydro-indazole cannabinoid (CB) modulator compounds and a method for use in treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease.

BACKGROUND OF THE INVENTION

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



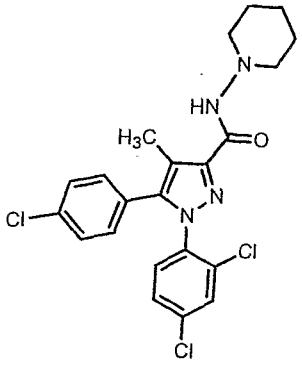
THC



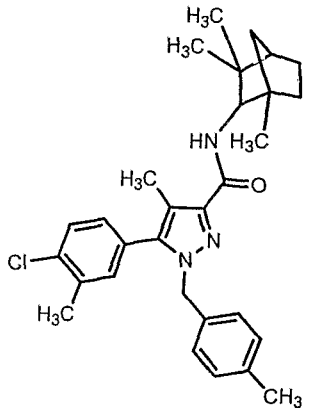
CANNABIDIOL

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

Pharmacological investigations have concentrated on selective CB receptor modulators of the pyrazole structural class, which include SR 141716A (the monohydrochloride salt of SR 141716) and SR 144528. SR 141716A was the first potent and selective CB1 receptor antagonist.



SR 141716



SR 144528

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

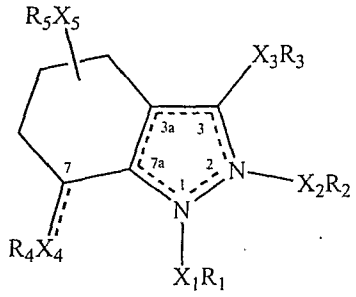
Certain compounds (including SR 141716, SR 144528 and the like) that were originally classified as selective antagonists are now considered to act as "inverse agonists" rather than pure antagonists. Inverse agonists have the ability to decrease the constitutive level of receptor activation in the absence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

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

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DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to a compound of formula I:



wherein

the dashed lines between positions 2-3 and positions 3a-7a in formula I represent locations for two double bonds present when X_1R_1 is present;

the dashed lines between positions 3-3a and positions 7a-1 in formula I represent locations for two double bonds present when X_2R_2 is present;

the dashed line between positions 7 and X_4R_4 in formula I represents the location for a double bond;

X_1 is absent, or is lower alkylene;

X_2 is absent, or is lower alkylene;

wherein only one of X_1R_1 and X_2R_2 are present;

X_3 is absent, or is lower alkylene, lower alkylidene or -NH-;

when the dashed line between positions 7 and X_4R_4 is absent, X_4 is absent, or is lower alkylene;

when the dashed line between positions 7 and X_4R_4 is present, X_4 is absent;

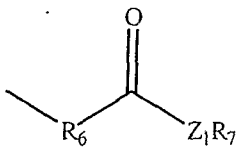
X_5 is absent, or is lower alkylene;

R_1 is selected from the group consisting of aryl, C_3-C_{12} cycloalkyl, or heterocyclyl, any of which are optionally substituted at one or more positions by halogen, lower alkyl, hydroxy or lower alkoxy;

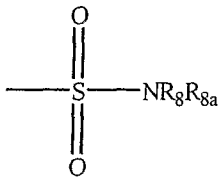
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R_2 is selected from the group consisting of aryl, C_3-C_{12} cycloalkyl, or heterocyclyl, any of which are optionally substituted at one or more positions by halogen, lower alkyl, hydroxy or lower alkoxy;

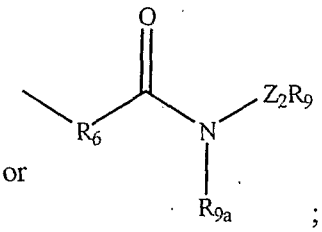
R_3 is



;



; or



;

when the dashed line between positions 7 and X_4R_4 is absent, R_4 is hydrogen; hydroxy; lower alkyl; lower alkoxy; halogen; aryl optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen; heterocyclyl optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen; or C_3-C_{12} cycloalkyl optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen;

when the dashed line between positions 7 and X_4R_4 is present, R_4 is CH-aryl wherein aryl is optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen; or CH-heterocyclyl wherein heterocyclyl is optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen;

R_5 is hydrogen; hydroxy; lower alkyl; lower alkoxy; hydroxy-lower alkylene-; carboxy; alkoxycarbonyl; aryloxycarbonyl; aryl-alkoxycarbonyl; NHR_{10}; $-C(O)NR_{11}R_{11a}$; $-O-C(O)-R_{12}$; oxo; or $-C(O)R_{13}$;

R_6 is absent, or is $-CH(R_{6a})-$;

R_{6a} is hydrogen; lower alkyl; or aryl optionally substituted by one or more of halogen, hydroxy, lower alkoxy, carboxy or alkoxycarbonyl;

R_7 is lower alkoxy; aryl optionally substituted by one or more hydroxy, halogen, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, hydroxy-alkylene-, $-NH(R_{6a})$, aryloxy, arylalkoxy, or aryl-lower alkylene; C_3-C_{12} cycloalkyl optionally substituted by one or more hydroxy, halogen, lower alkyl, lower

alkyl-aminocarbonyl, carboxy, alkoxycarbonyl, lower alkoxy, lower alkoxy-lower alkylene-, hydroxy-alkylene-, aryloxy, arylalkoxy, arylalkoxy-lower alkylene- optionally substituted on aryl by one or more hydroxy, halogen or lower alkyl; or aryl-lower alkylene; heterocyclyl optionally substituted by one or more hydroxy, halogen, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, lower alkoxy-lower alkylene-, hydroxy-alkylene-, aryloxy or arylalkoxy;

R_8, R_{8a}, R_9 and R_{9a} are each individually hydrogen; lower alkyl; $-NHR_{15}$; aryl optionally substituted by one or more hydroxy, halogen, $-NH(R_{6a})$, $-SO_2-NH(R_{6a})$, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, hydroxy-alkylene-, aryloxy or arylalkoxy; C_3-C_{12} cycloalkyl optionally substituted by one or more hydroxy, halogen, amino, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, hydroxy-alkylene-, aryloxy, arylalkoxy, or lower alkylene; or heterocyclyl optionally substituted by one or more hydroxy, halogen, amino, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, hydroxy-alkylene-, aryloxy or arylalkoxy;

R_{10} is hydrogen, C_1-C_{10} alkoxycarbonyl optionally substituted at one or more positions by hydroxy, halogen or aryl; $-C(O)CF_3$; $-SO_2-NR_{14}R_{14a}$; -C(O)-heterocyclyl optionally substituted at one or more positions by hydroxy, halogen or aryl; $-C(O)NR_{14}R_{14a}$; $-SO_2$-aryl; $-SO_2R_{14}$; or $SO_2NR_{14}R_{14a}$;

R_{11}, R_{11a}, R_{12}, R_{13}, R_{14} and R_{14a} and R_{15} are each individually hydrogen; C_1-C_{10} alkyl; heterocyclyl; C_3-C_{12} cycloalkyl; or aryl optionally substituted by lower alkyl, hydroxy, alkoxy, halogen $-SO_2-N(R_{6a})_2$, heterocyclyl or aryl-lower alkylene-;

Z_1 is absent; -NH-; or is lower alkylene optionally substituted at one or more positions by halogen, hydroxy, lower alkoxy, carboxy or lower alkoxycarbonyl;

Z_2 is absent; or is lower alkylene optionally substituted at one or more positions by aryl, cycloalkyl, halogen, hydroxy, lower alkyl, lower alkoxy, carboxy, alkoxycarbonyl or aryl;

or a pharmaceutically acceptable salt, isomer, prodrug, metabolite or polymorph thereof.

An example of the present invention is a compound of formula (I) wherein X_1 is absent, or is lower alkylene, and R_1 is C_3-C_{12} cycloalkyl; or aryl optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen.

An example of the present invention is a compound of formula (I) wherein the dashed line between positions 7 and X_4R_4 is absent; X_4 is absent, or is lower alkylene; and, R_4 is hydrogen; hydroxy; lower alkyl; lower alkoxy; halogen; aryl optionally substituted at one or more positions by lower alkoxy or halogen; heterocyclyl optionally substituted at one or more positions by halogen; or C_3-C_8 cycloalkyl.

An example of the present invention is a compound of formula (I) wherein the dashed line between positions 7 and X_4R_4 is absent; X_4 is absent; and, R_4 is hydrogen.

An example of the present invention is a compound of formula (I) wherein R_3 is $-R_6C(O)NHZ_2R_9$; R_6 is absent; Z_2 is absent; or is lower alkylene optionally substituted by lower alkyl, lower alkoxy, carboxy, lower alkoxycarbonyl, hydroxy or halogen; and, R_9 is aryl optionally substituted by one or more hydroxy, halogen, $-NH(R_{6a})$, $-SO_2-NH(R_{6a})$, lower alkyl, lower alkoxy or arylalkoxy; C_5-C_{12} cycloalkyl optionally substituted at one or more positions by lower alkyl, lower alkoxy, hydroxy, amino, halogen or lower alkoxycarbonyl; or heterocyclyl.

An example of the present invention is a compound of formula (I) wherein R_3 is $-R_6C(O)Z_1R_7$; R_6 is absent; and, R_7 is lower alkoxy; aryl optionally substituted by one or more hydroxy, lower alkoxy, $-NH(R_{6a})$ or arylalkoxy; C_3-C_{12} cycloalkyl optionally substituted by one or more lower alkyl, lower alkyl-aminocarbonyl, carboxy, alkoxycarbonyl, lower alkoxy-lower alkylene-, hydroxy-alkylene-, arylalkoxy-lower alkylene- optionally substituted on aryl by one or more halogen; or heterocyclyl optionally substituted by one or more lower alkyl, alkoxycarbonyl or lower alkoxy-lower alkylene-.

An example of the present invention is a compound of formula (I) wherein X_3 is lower alkylidene; R_3 is $-SO_2NHR_8$; and, R_8 is aryl or C_5-C_{12} cycloalkyl.

An example of the present invention is a compound of formula (I) wherein X_2 is absent, or is lower alkylene; and, R_2 is C_3-C_{12} cycloalkyl; or aryl optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen.

An example of the present invention is a compound of formula (I) wherein the dashed line between positions 7 and X_4R_4 is present, X_4 is absent; and, R_4 is CH-aryl wherein aryl is optionally substituted at one or more positions by hydroxy, lower alkyl,

lower alkoxy or halogen; or CH-heterocyclyl wherein heterocyclyl is optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen.

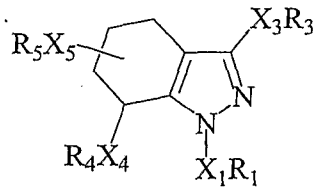
An example of the present invention is a compound of formula (I) wherein the dashed line between positions 7 and X_4R_4 is present, X_4 is absent; and, R_4 is CH-aryl wherein aryl is optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen; or CH-heterocyclyl, wherein heterocyclyl is optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen.

An example of the present invention is a compound of formula (I) wherein the dashed line between positions 7 and X_4R_4 is present, X_4 is absent; and, R_4 is CH-phenyl, CH-thienyl or CH-furyl, wherein phenyl, thienyl or furyl is each optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen.

An example of the present invention is a compound of formula (I) wherein X_5 is absent; and, R_5 is hydrogen; hydroxy; lower alkyl; hydroxy-lower alkylene-; carboxy; lower alkoxycarbonyl; aryl-alkoxycarbonyl; NHR_{10}; $-C(O)NR_{11}R_{11a}$; $-O-C(O)-R_{12}$; or oxo.

An example of the present invention is a compound of formula (I) wherein R_{10} is hydrogen; C_1-C_{10} alkoxycarbonyl; $-C(O)CF_3$; -C(O)-heterocyclyl; $-C(O)NR_{14}R_{14a}$; or $-SO_2NR_{14}R_{14a}$; and wherein R_{11}, R_{11a}, R_{12}, R_{14} and R_{14a} are each individually hydrogen; C_1-C_{10} alkyl; or aryl optionally substituted by lower alkyl, heterocyclyl or aryl-lower alkylene-.

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



wherein X_1R_1, X_3R_3, X_4R_4 and X_5R_5 are dependently selected from

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
1	phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
2	(4-OCH_3)-phenyl	C(O)NHN[(CH_2CH_3)(2-OCH_3-phenyl)]	H	H
3	(4-OCH_3)-phenyl	C(O)NHCH$(CO_2CH_3)CH_2$-(3-OCH_2-phenyl)phenyl	H	H

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
5	(4-OCH_3)-phenyl	C(O)NHCH(CO_2CH_3)CH_2-(4-OH)phenyl	H	H
7	(4-OCH_3)-phenyl	C(O)NH$(CH_2)_2$-(4-NH_2)phenyl	H	H
9	(4-OCH_3)-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
10	(4-F)phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
11	(4-CH_3)-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
12	(4-Cl)-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
13	(4-F)phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	CH_3
14	(4-F)phenyl	C(O)NHCH_2-6,6-$(CH_3)_2$-bicyclo[3.1.1]hept-2-yl	H	H
15	(4-F)phenyl	C(O)NH-cyclooctyl	H	H
16	(2-F)phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
17	(2-F)phenyl	C(O)NHCH_2-6,6-$(CH_3)_2$-bicyclo[3.1.1]hept-2-yl	H	H
18	(3-F)phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
19	(3-F)phenyl	C(O)NHCH_2-6,6-$(CH_3)_2$-bicyclo[3.1.1]hept-2-yl	H	H
20	(4-F)phenyl	C(O)NH-bicyclo[2.2.1]hept-2-yl	H	H
21	(4-F)phenyl	C(O)NH-1,7,7-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
22	(4-F)phenyl	C(O)NHCH(CH_3)-adamantan-2-yl	H	H
23	(4-F)phenyl	C(O)NH-3-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-2-yl	H	H
24	(4-F)phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	cyclohexyl
25	cyclohexyl	C(O)NH-1,7,7-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
26	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	H	H
27	cycloheptyl	C(O)NH-(2*R*)-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
28	cyclohexyl	C(O)NH-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
29	CH_2-phenyl	C(O)NHNH(cyclohexyl)	H	H
30	(4-F)phenyl	C(O)NHNH(cyclohexyl)	H	H
31	cyclohexyl	C(O)NHNH(cyclohexyl)	H	H
32	cyclohexyl	C(O)NHCH_2-adamantan-1-yl	H	H

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
33	(4-F)phenyl	C(O)NH-(1*S*,2*R*)-2-$CO_2CH_2CH_3$-cyclohexyl	H	H
34	(4-F)phenyl	C(O)NH-(1*R*,2*R*)-2-$CO_2CH_2CH_3$-cyclohexyl	H	H
35	(4-F)phenyl	C(O)NH-azepan-1-yl	H	H
36	cyclohexyl	C(O)NH-(1*S*,2*R*)-2-$CO_2CH_2CH_3$-cyclohexyl	H	H
37	cyclohexyl	C(O)NH-azepan-1-yl	H	H
38	CH_2-phenyl	C(O)NH-(1*S**,2*R**)-2-$CO_2CH_2CH_3$-cyclohexyl	H	H
39	CH_2-phenyl	C(O)NHCH(CH_3)-adamantan-1-yl	H	H
40	cyclohexyl	C(O)NH-2-CH_2OH-bicyclo[2.2.1]hept-3-yl	H	H
41	CH_2-phenyl	C(O)NH-azepan-1-yl	H	H
43	CH_2-phenyl	C(O)NH-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
44	cyclohexyl	C(O)NH-adamantan-1-yl	H	H
45	cyclohexyl	C(O)NH-adamantan-2-yl	H	H
46	cyclohexyl	C(O)NH-8-CH_3-8-aza-bicyclo[3.2.1]oct-3-yl	H	H
47	cyclohexyl	C(O)NH-2-CH_2OH-bicyclo[2.2.1]hept-3-yl	H	H
48	cyclohexyl	C(O)NH-(1*R**,2*S**)-2-CH_2OH-cyclohexyl	H	H
49	cyclohexyl	C(O)NH-(1*R**,2*R**)-2-CH_2OH-cyclohexyl	H	H
50	cyclohexyl	$(CH_2)_2$C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
51	cyclohexyl	$(CH_2)_2$C(O)NH-(1*R**,2*R**)-2-CH_2OH-cyclohexyl	H	H
52	cyclohexyl	$(CH_2)_2$C(O)NH-(2*S*,3*R*)-2-CH_2OH-bicyclo[2.2.1]hept-3-yl	H	H
53	cyclohexyl	$(CH_2)_2$C(O)NHCH(CH_3)-adamantan-1-yl	H	H
54	cyclohexyl	$(CH_2)_2$C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
55	cyclohexyl	C(O)NH-3-$CO_2CH_2CH_3$-5,6,7,8-tetrahydro-4*H*-cyclohepta(*b*)thien-2-yl	H	H
56	cyclohexyl	C(O)NH-3-$CO_2CH_2CH_3$-5,6-dihydro-4*H*-cyclopenta(*b*)thien-2-yl	H	H
57	cyclohexyl	C(O)NH-2-$CO_2CH_2CH_3$-cyclopent-1-en-1-yl	H	H
58	cyclohexyl	C(O)NH-(1*R*,2*S*)-2-$CO_2CH_2CH_3$-cyclopentyl	H	H
59	cyclohexyl	C(O)NH-(1*S*,2*S*)-2-$CO_2CH_2CH_3$-cyclohexyl	H	H
60	cyclohexyl	C(O)NH-(1*S**,2*R**)-2-CH_2OH-cyclohexyl	H	Cl
61	cyclohexyl	C(O)NH-(1*S**,2*R**)-2-$CO_2CH_2CH_3$-cyclopentyl	H	Cl
62	cyclohexyl	C(O)NH-adamantan-2-yl	H	Cl
63	cyclohexyl	C(O)NH-(2*S**,3*R**)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	Cl

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
64	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	H	Cl
65	cyclohexyl	$CH_2C(CH_3)_2C(O)NHCH(CH_3)$-adamantan-1-yl	H	H
66	cyclohexyl	$CH_2C(CH_3)_2C(O)NH$-adamantan-2-yl	H	H
67	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-CO_2-CH_2CH_3	H
68	cyclohexyl	C(O)NH-adamantan-2-yl	6-CO_2-CH_2CH_3	H
69	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	6-CO_2-CH_2CH_3	H
70	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	6-CO_2-CH_2CH_3	H
71	cyclohexyl	C(O)NH-adamantan-2-yl	4-CO_2-CH_2CH_3	H
72	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	4-CO_2-CH_2CH_3	H
73	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	4-CO_2-CH_2CH_3	H
74	cycloheptyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
75	CH_2-phenyl	C(O)NHCH(CO_2CH_3)CH_2-(4-OH)phenyl	H	H
76	CH_2-phenyl	C(O)NHCH(CO_2H)CH_2-(4-OCH_2-phenyl)phenyl	H	H
77	cyclohexyl	C(O)NHCH(CO_2CH_3)CH_2-(4-OH)phenyl	H	H
78	cyclohexyl	C(O)NHCH(CO_2H)CH_2-(4-OCH_2-phenyl)phenyl	H	H
79	cyclohexyl	C(O)NH-adamantan-2-yl	5-CO_2CH_2-phenyl	H
80	CH_2-phenyl	C(O)NHCH(CO_2CH_3)CH_2-(4-OCH_2-phenyl)phenyl	H	H
81	cyclohexyl	C(O)NHCH(CO_2CH_3)CH_2-(4-OCH_2-phenyl)phenyl	H	H
82	CH_2-phenyl	C(O)NHCH(CO_2CH_3)CH_2-(3,4-$(OH)_2$-phenyl)	H	H
83	CH_2-phenyl	C(O)NHCH(CO_2CH_3)CH_2-1*H*-indol-3-yl	H	H
85	cyclohexyl	C(O)NH-adamantan-2-yl	5-$NHCO_2$-$C(CH_3)_3$	H
86	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-$NHCO_2$-$C(CH_3)_3$	H
87	cyclohexyl	C(O)NH-adamantan-2-yl	5-NHC(O)-CF_3	H
88	cyclohexyl	C(O)NH-adamantan-2-yl	5-NH-CO_2CH_3	H
89	cyclohexyl	C(O)NH-adamantan-2-yl	5-NHC(O)-$N(CH_3)_2$	H

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
90	cyclohexyl	C(O)NH-adamantan-2-yl	5-NHC(O)-morpholin-4-yl	H
92	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-NH_2	H
93	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-OH	H
94	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-OC(O)-CH_3	H
95	cyclohexyl	C(O)NH-adamantan-2-yl	5-C(O)NH-[1,2,4]-triazol-4-yl	H
96	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-oxo	H
97	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-oxo	H
98	cyclohexyl	C(O)NH-adamantan-2-yl	5-$C(CH_3)_3$	H
99	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-$C(CH_3)_3$	H
100	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-$C(CH_3)_3$	H
101	cyclohexyl	C(O)NH-octahydro-2,5-methano-pentalen-3a-yl	5-$C(CH_3)_3$	H
102	cyclohexyl	C(O)NHCH_2-adamantan-1-yl	5-$C(CH_3)_3$	H
103	cyclohexyl	C(O)NH-adamantan-2-yl	5-NHC(O)-N[(CH_3)-phenyl]	H
104	cyclohexyl	C(O)NH-adamantan-2-yl	5-NH-SO_2CH_3	H
105	cyclohexyl	C(O)NH-adamantan-2-yl	5-NHSO_2-(4-CH_3)-phenyl	H
106	cyclohexyl	C(O)NH-adamantan-2-yl	5-NHSO_2-N(CH_3)$_2$	H
107	cyclohexyl	C(O)NH-(2*S*,3*R*)-2-$CH_2OCH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
108	cyclohexyl	C(O)NH-(2*S*,3*R*)-2-CH_2OCH_2-(2-Br-phenyl)-bicyclo[2.2.1]hept-3-yl	H	H
109	phenyl	C(O)NH-adamantan-2-yl	5-$C(CH_3)_3$	H
110	phenyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-$C(CH_3)_3$	H
111	phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-$C(CH_3)_3$	H
112	phenyl	C(O)NHCH_2-adamantan-1-yl	5-$C(CH_3)_3$	H
113	phenyl	C(O)NH-adamantan-1-yl	5-$C(CH_3)_3$	H
114	phenyl	C(O)NHCH(CH_3)-(1*R*)-cyclohexyl	5-$C(CH_3)_3$	H
115	phenyl	C(O)NH-adamantan-2-yl	5-CO_2-CH_2CH_3	H

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
116	phenyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-CO_2-CH_2CH_3	H
117	phenyl	C(O)NHCH_2-adamantan-1-yl	5-CO_2-CH_2CH_3	H
118	phenyl	C(O)NH-adamantan-1-yl	5-CO_2-CH_2CH_3	H
119	CH_2-phenyl	C(O)NH-6-$CO_2CH_2CH_3$-cyclohex-3-en-1-yl	H	H
120	cyclohexyl	C(O)NH-6-$CO_2CH_2CH_3$-cyclohex-3-en-1-yl	H	OCH_3
122	CH_2-cyclohexyl	C(O)NH-adamantan-2-yl	H	H
123	CH_2-cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	H	H
124	CH_2-cyclohexyl	C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
125	CH_2-(4-CH_3)-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
126	CH_2-(4-CH_3)-phenyl	C(O)NH-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
127	CH_2-phenyl	C(O)NH-cyclooctyl	H	H
128	cyclohexyl	C(O)NH-cyclooctyl	H	H
129	(2,4-Cl_2)-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
130	(2,4-Cl_2)-phenyl	C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
131	(2,4-Cl_2)-phenyl	C(O)NH-adamantan-2-yl	H	H
132	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-CO_2-CH_2CH_3	H
133	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-CO_2H	H
134	(2,4-Cl_2)-phenyl	C(O)NH-azepan-1-yl	H	H
135	CH_2-phenyl	C(O)NHCH_2-adamantan-1-yl	H	H
136	CH_2-phenyl	C(O)NH-adamantan-2-yl	H	H
137	cyclohexyl	C(O)NH-3-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-2-yl	5-CO_2-CH_2CH_3	H
138	cyclohexyl	C(O)NH-3-CH_2OH-bicyclo[2.2.1]hept-2-yl	5-CO_2H	H
139	(2,4-Cl_2)-phenyl	C(O)NH-adamantan-1-yl	H	H
141	(2,4-Cl_2)-phenyl	C(O)NHCH_2-adamantan-1-yl	H	H
143	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-CH_2OH	H
144	(4-F)phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	phenyl
145	(4-F)phenyl	C(O)NHCH_2-adamantan-1-yl	H	phenyl

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
146	(4-F)phenyl	C(O)NHCH(CH_3)-adamantan-1-yl	H	phenyl
147	(4-F)phenyl	C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	phenyl
148	CH_2-phenyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-CO_2-CH_2CH_3	H
149	CH_2-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-CO_2-CH_2CH_3	H
150	(4-F)phenyl	C(O)NH-adamantan-1-yl	H	$(CH_2)_2$-phenyl
151	(4-F)phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	$(CH_2)_2$-phenyl
152	(4-F)phenyl	C(O)NHCH_2-adamantan-1-yl	H	$(CH_2)_2$-phenyl
153	(4-F)phenyl	C(O)NHCH(CH_3)-adamantan-1-yl	H	$(CH_2)_2$-phenyl
154	(4-F)phenyl	C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	$(CH_2)_2$-phenyl
155	CH_2-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-CO_2H	H
156	CH_2-phenyl	C(O)NHCH_2-adamantan-1-yl	6-CO_2-CH_2CH_3	H
157	CH_2-phenyl	C(O)NH-octahydro-2,5-methano-pentalen-3a-yl	6-CO_2-CH_2CH_3	H
158	CH_2-phenyl	C(O)NH-adamantan-2-yl	4-CO_2-CH_2CH_3	H
159	CH_2-phenyl	C(O)NHCH_2-adamantan-1-yl	4-CO_2-CH_2CH_3	H
160	pyridin-2-yl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
161	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	H	OCH_3
162	cyclohexyl	C(O)NH-adamantan-2-yl	H	OCH_3
163	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	H	OH
164	cyclohexyl	C(O)NH-(2*S**,3*R**)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	OH
165	(4-F)phenyl	C(O)NH-adamantan-1-yl	H	phenyl
166	CH_2-phenyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-CO_2H	H
167	CH_2-phenyl	C(O)NH-(2*R**,3*S**)-2-C(O)NHCH_2CH_3-bicyclo[2.2.1]hept-3-yl	H	H
168	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-CO_2H	H
169	cycloheptyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-CO_2CH_3	H
170	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-C(O)-NH_2	H

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
171	CH_2-phenyl	C(O)NH-1-$CO_2CH_2CH_3$-piperidin-4-yl	H	H
172	(4-F)phenyl	C(O)NH-1-CO_2H-cyclohexyl	H	H
173	cyclohexyl	C(O)NHCH_2-pyridin-3-yl	H	H
174	CH_2-phenyl	C(O)NH$(CH_2)_2$-morpholin-4-yl	H	H
175	CH_2-phenyl	C(O)NH$(CH_2)_2$-morpholin-4-ium	H	H
176	cyclohexyl	C(O)NHCH_2C(O)-(4-OCH_3)phenyl	H	H
177	cyclohexyl	C(O)NHCH_2C(O)-(4-Br)phenyl	H	H
178	cyclohexyl	NHC(O)naphthalen-2-yl	H	H
179	cyclohexyl	NHC(O)adamantan-1-yl	H	H
180	cyclohexyl	NHC(O)cyclohexyl	H	H
181	cyclohexyl	NHC(O)naphthalen-1-yl	H	H
182	cyclohexyl	NHC(O)NH-adamantan-1-yl	H	H
183	cyclohexyl	C(O)NH-1,2,3,4-tetrahydro-naphthalen-1-yl	H	H
184	cyclohexyl	C(O)NHCH(CH_3)-cyclohexyl	H	H
185	cyclohexyl	C(O)NHCH_2CH(OH)-cyclohexyl	H	H
186	cyclohexyl	NHC(O)phenyl	H	H
187	cyclohexyl	C(O)NHCH_2C(O)-cyclohexyl	H	H
188	cyclohexyl	C(O)NHCH_2C(O)-phenyl	H	H
189	CH_2-phenyl	C(O)NHCH_2-cyclohexyl	H	H
191	(4-F)phenyl	C(O)NH-(2*S**,3*R**)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	CH_2CH_3
192	(4-F)phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	CH_2CH_3
193	cyclohexyl	C(O)NHCH(CH_3)-cyclopentyl	H	H
194	CH_2-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
195	cyclohexyl	C(O)NHCH-(*R*-CH_3)-cyclohexyl	H	H
196	cyclohexyl	C(O)NHCH-(*S*-CH_3)-phenyl	H	H
197	cyclohexyl	C(O)NHCH-(*R*-CH_3)-phenyl	H	H
198	CH_2-phenyl	C(O)NHCH-(*R*-CH_3)-cyclohexyl	H	H
199	CH_2-phenyl	C(O)NHCH-(*R*-CH_3)-phenyl	H	H
200	CH_2-phenyl	C(O)NHCH-(*S*-CH_3)-phenyl	H	H
201	CH_2-phenyl	C(O)NHCH-(*S*-CH_3)-cyclohexyl	H	H
202	(4-F)phenyl	C(O)NH-(2*S*)-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
203	cyclohexyl	C(O)N[(CH_2CH_3)[CH(*R*-CH_3)cyclohexyl]]	H	H
204	cyclohexyl	C(O)NHCH-(*R*-CH_2CH_3)-phenyl	H	H
205	cyclohexyl	NHC(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
206	CH_2-phenyl	C(O)NH-(2*R**,3*S**)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-5-en-3-yl	H	H
207	cyclohexyl	C(O)NH-(2*S**)-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
208	cyclohexyl	C(O)NH-adamantan-2-yl	5*S**-CO_2-CH_2CH_3	H
209	cyclohexyl	C(O)NH-adamantan-2-yl	5*R**-CO_2-CH_2CH_3	H
210	CH_2-phenyl	C(O)NH-adamantan-2-yl	5*S**-CO_2-CH_2CH_3	H
211	CH_2-phenyl	C(O)NH-adamantan-2-yl	5*R**-CO_2-CH_2CH_3	H
212	cyclohexyl	C(O)NHCH-(*R**-CH_3)-adamantan-1-yl	H	H
213	cyclohexyl	C(O)NHCH-(*S**-CH_3)-adamantan-1-yl	H	H
214	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	5*R**-CO_2-CH_2CH_3	H
215	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	5*S**-CO_2-CH_2CH_3	H
216	cyclohexyl	C(O)NH-(2*S**,3*S**)-2-CH_3-6,6-$(CH_3)_2$-bicyclo[3.1.1]hept-3-yl	H	H
217	CH_2-phenyl	C(O)NH-(2*R**)-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
218	cyclohexyl	C(O)NH-adamantan-2-yl	5*S**-CO_2-CH_3	H
219	cyclohexyl	C(O)NH-adamantan-2-yl	5*R**-CO_2-CH_3	H
220	phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5*R**-CO_2-CH_2CH_3	H
222	cyclohexyl	C(O)NH-adamantan-2-yl	5-CO_2-CH_2CH_3	H
223	cyclohexyl	C(O)NH-adamantan-2-yl	5-CO_2H	H
224	cyclohexyl	C(O)NHCH(CH_3)-adamantan-1-yl	5-$C(O)NH_2$	H
225	cyclohexyl	C(O)NH-1-aza-bicyclo[2.2.2]oct-3-yl	H	H
226	CH_2-phenyl	C(O)NH-adamantan-2-yl	5-CO_2-CH_2CH_3	H
228	cyclohexyl	C(O)NH-adamantan-2-yl	5-C(O)NH-$C(CH_3)_2$-CH_2-$C(CH_3)_3$	H
229	cyclohexyl	C(O)NH-piperidin-1-yl	5-CO_2-CH_2CH_3	H
230	CH_2-phenyl	C(O)NH-adamantan-2-yl	6-CO_2-CH_2CH_3	H
231	cyclohexyl	C(O)NH-adamantan-2-yl	5-CO_2CH_3	H

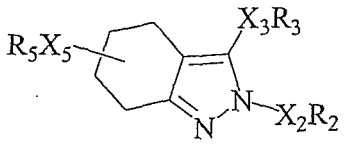
Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
232	cyclohexyl	C(O)NH-adamantan-2-yl	5-CO_2-$CH(CH_3)_2$	H
233	cyclohexyl	C(O)NH-adamantan-2-yl	5-CO_2-$C(CH_3)_3$	H
234	cyclohexyl	C(O)NHCH(CH_2CH_3)-cyclohexyl	H	H
235	cyclohexyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	5-C(O)-$N(CH_3)_2$	H
236	cyclohexyl	C(O)NH$(CH_2)_2$-(2-OCH_3)phenyl	H	H
237	CH_2-phenyl	C(O)NH$(CH_2)_2$-(2-OCH_3)phenyl	H	H
238	phenyl	C(O)NH$(CH_2)_2$-(2-OCH_3)phenyl	H	H
239	CH_2-phenyl	C(O)NH-adamantan-2-yl	5-CO_2H	H
240	cyclohexyl	C(O)NHCH_2CH(OH)-(4-Br)phenyl	H	H
241	cyclohexyl	C(O)NHCH_2CH(OH)-(4-OCH_3)phenyl	H	H
242	CH(CH_3)-phenyl	C(O)NHCH_2-cyclohexyl	H	H
243	CH(CH_3)-phenyl	C(O)NH-adamantan-2-yl	H	H
244	CH(CH_3)-phenyl	C(O)NH-adamantan-1-yl	H	H
245	cyclohexyl	C(O)NH-2-CH_3-cyclohexyl	H	H
246	cyclohexyl	C(O)NHCH(CH_3)-cycloheptyl	H	H
247	cyclohexyl	C(O)NHCH(CH_3)-cyclobutyl	H	H
248	cyclohexyl	C(O)NHCH(CH_3)-(1*R*,4*R*)-4-CH_3-cyclohexyl	H	H
249	CH(CH_3)-phenyl	C(O)NHCH(CH_3)-cyclohexyl	H	H
250	CH(CH_3)-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
251	cyclohexyl	C(O)NH-(*R**-CH)(CH_3)-cyclohexyl	5-CO_2-CH_2CH_3	H
252	cyclohexyl	C(O)NH-(2*R**,3*R**)-2-CH_3-6,6-$(CH_3)_2$-bicyclo[3.1.1]hept-3-yl	H	H
253	CH_2-phenyl	C(O)NHCH(CH_3)-phenyl	H	phenyl
254	CH_2-phenyl	C(O)NH-3-CH_2OCH_3-pyrrolidin-1-yl	H	phenyl
255	CH_2-phenyl	C(O)NH-phenyl	H	phenyl
256	CH_2-phenyl	C(O)NH-CH(CH_3)-phenyl	5-CO_2-CH_2CH_3	H
257	cyclohexyl	C(O)NH-CH(CH_3)-phenyl	5-CO_2-CH_2CH_3	H
258	(4-F)phenyl	$(CH)_2$-SO_2NH-CH(CH_3)-phenyl	H	$(CH_2)_2$-phenyl
259	(4-F)phenyl	$(CH)_2$-SO_2NH-CH(CH_3)-cyclohexyl	H	$(CH_2)_2$-phenyl

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
260	CH_2-phenyl	$(CH)_2$-SO_2NH-CH(*R*-CH_3)-phenyl	H	H
261	CH_2-phenyl	$(CH)_2$-SO_2NH-CH(*S*-CH_3)-phenyl	H	H
262	CH_2-phenyl	$(CH)_2$-SO_2NH-CH(*R*-CH_3)-cyclohexyl	H	H
263	CH_2-phenyl	$(CH)_2$-SO_2NH-CH(*S*-CH_3)-cyclohexyl	H	H
264	CH_2-phenyl	*C(O)NH-1-*$CO_2C(CH_3)_3$*-piperidin-4-yl*	H	H
265	CH_2-phenyl	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	phenyl
266	CH_2-phenyl	C(O)NH-piperidin-1-yl	H	phenyl
267	CH_2-phenyl	C(O)NHCH(CH_3)-cyclohexyl	H	phenyl
268	CH_2-phenyl	C(O)NH-azepan-1-yl	H	phenyl
269	cyclohexyl	*C(O)NH-(1R,2R)-2-*$CO_2CH_2CH_3$-cyclohexyl	H	H
272	CH_2-phenyl	*C(O)NH-(2R-*$CO_2CH_2CH_3$*)-(R)-cyclohexyl*	H	H
274	CH_2-phenyl	C(O)NH-(2*R**,3*S**)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl		
276	CH_2-phenyl	C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-5-en-3-yl	H	H
278	cyclohexyl	C(O)NH-(2*R*,3*S*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
279	cyclohexyl	C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-5-en-3-yl	H	H
280	cyclohexyl	C(O)NH-(2*R*,3*S*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-5-en-3-yl	H	H
281	cyclohexyl	$CH_2C(CH_3)_2$C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	H
282	cyclohexyl	*C(O)NH-(2S,3R)-2-*$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl	H	OCH_3
283	(2,4-Cl_2)-phenyl	*C(O)NHCH(*CH_3*)-adamantan-1-yl*	H	H
284	cyclohexyl	C(O)NH-(*R**-CH)(CH_3)-cyclohexyl	6-CO_2-CH_2CH_3	H
285	cyclohexyl	*C(O)NH-(R*-*CH)(CH_3)-cyclohexyl	4-CO_2-CH_2CH_3	H
286	cyclohexyl	C(O)NH-(*R**-CH)(CH_3)-cyclohexyl	5-$NHCO_2$-$C(CH_3)_3$	H
287	(2,4-Cl_2)-phenyl	*C(O)NH-piperidin-1-yl*	H	H
288	cyclohexyl	C(O)NHCH-(*R*-CH_3)-phenyl	5-CO_2-CH_2CH_3	H
289	CH_2-phenyl	C(O)NH-(*R*-CH)(CH_3)-cyclohexyl	5-CO_2-CH_2CH_3	H
299	*(4-F)phenyl*	*C(O)NHNH(cyclooctyl)*	H	H
300	cyclohexyl	*C(O)NHNH(cyclooctyl)*	H	H
301	cyclohexyl	C(O)NH-6-$CO_2CH_2CH_3$-cyclohex-3-en-1-yl	H	H

Cpd	X_1R_1	X_3R_3	X_5R_5	X_4R_4
302	cyclohexyl	C(O)NH-(2*S**,3*R**)-2-CH_2OH-bicyclo[2.2.1]hept-3-yl	H	H
303	cyclohexyl	C(O)NHCH_2-pyridin-4-yl	H	H
304	cyclohexyl	C(O)NHCH_2-cyclohexyl	H	H
305	CH_2-phenyl	$(CH)_2$-C(O)NH-CH(*S*-CH_3)-phenyl	H	H
306	CH_2-phenyl	$(CH)_2$-C(O)NH-CH(*R*-CH_3)-phenyl	H	H
312	(2,4-Cl_2)-phenyl	C(O)NHCH(*R*-CH_3)-phenyl	H	(3-OCH_3)-phenyl
313	(2,4-Cl_2)-phenyl	C(O)NHCH(*S*-CH_2OH)-phenyl	H	(3-OCH_3)-phenyl
314	(2,4-Cl_2)-phenyl	C(O)NHCH(*R*-CH_2OH)-phenyl	H	(3-OCH_3)-phenyl
315	(2,4-Cl_2)-phenyl	C(O)NHCH(*R*-CH_2Cl)-phenyl	H	(3-OCH_3)-phenyl
316	(2,4-Cl_2)-phenyl	C(O)NHCH(*S*-CH_2Cl)-phenyl	H	(3-OCH_3)-phenyl
317	(2,4-F_2)-phenyl	C(O)NHCH(*R*-CH_3)-phenyl	H	(3-OCH_3)-phenyl
318	(2,4-F_2)-phenyl	C(O)NHCH(*R*-CH_2OH)-phenyl	H	(3-OCH_3)-phenyl
326	cyclohexyl	C(O)NH-adamantan-2-yl	5-C(O)-N(CH_2-phenyl)$_2$	H
327	cyclohexyl	C(O)NH-adamantan-2-yl	5-C(O)NH-$(CH_2)_2CH_3$	H
328	cyclohexyl	C(O)N(CH_3)CH(*R*-CH_3)cyclohexyl	H	H
329	cyclohexyl	C(O)N[$CH(CH_3)_2$]CH(*R*-CH_3)-cyclohexyl	H	H
330	cyclohexyl	C(O)NHCH(CH_3)CH_2-cyclohexyl	H	H
331	cyclohexyl	C(O)NHCH(phenyl)-cyclohexyl	H	H
332	cyclohexyl	$CH_2CH(CO_2CH_2CH_3)$-(2-OCH_3)-phenyl	H	H
333	cyclohexyl	CH_2CH(2-OCH_3-phenyl)-C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H
334	cyclohexyl	NHC(O)NH-CH(CH_3)-cyclohexyl	H	H
335	CH_2-phenyl	C(O)N(CH_3)(phenyl)	H	phenyl
336	cyclohexyl	$NHSO_2$-(4-CH_3)phenyl	H	H
337	CH_2-phenyl	NHC(O)NH-adamantan-1-yl	H	H
338	CH_2-phenyl	NHC(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl	H	H

and pharmaceutically acceptable forms thereof.

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

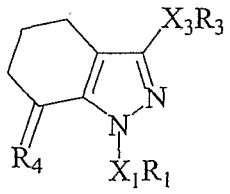


wherein X_2R_2, X_3R_3 and X_5R_5 are dependently selected from

Cpd	X_2R_2	X_5R_5	X_3R_3
4	(4-OCH_3)-phenyl	H	C(O)NHCH(CO_2CH_3)CH_2-(4-OCH_2-phenyl)phenyl
6	(4-OCH_3)-phenyl	H	C(O)NHCH(CO_2CH_3)CH_2-(4-OH)phenyl
8	(4-OCH_3)-phenyl	H	C(O)NH$(CH_2)_2$-(4-NH_2)phenyl
42	CH_2-phenyl	H	C(O)NH-(2-$CO_2CH_2CH_3$)-bicyclo[2.2.1]hept-3-yl
84	cyclohexyl	5-$NHCO_2C(CH_3)_3$	C(O)NH-adamantan-2-yl
91	phenyl	5-$CO_2CH_2CH_3$	C(O)NH-adamantan-1-yl
121	(4-OCH_3)-phenyl	H	C(O)N-(CH_2CH_3)-(2-OCH_3)phenyl
140	(2,4-Cl_2)-phenyl	H	C(O)NH-adamantan-1-yl
142	(2,4-Cl_2)-phenyl	H	C(O)NHCH_2-adamantan-1-yl
190	cyclohexyl	5-$CO_2CH_2CH_3$	C(O)NHCH(CH_3)-adamantan-1-yl
221	cyclohexyl	5-$CO_2CH_2CH_3$	C(O)NH-adamantan-2-yl
227	CH_2-phenyl	5-$CO_2CH_2CH_3$	C(O)NH-octahydro-2,5-methano-pentalen-3a-yl
270	CH_2-phenyl	H	C(O)NH-(1*S**,2*R**)-2-$CO_2CH_2CH_3$-cyclohexyl
271	CH_2-phenyl	H	C(O)NH-(1*S*,2*S*)-2-$CO_2CH_2CH_3$-cyclohexyl
273	CH_2-phenyl	H	C(O)NH-(2*R*,3*S*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-3-yl
275	CH_2-phenyl	H	C(O)NH-(2*S*,3*R*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-5-en-3-yl
277	CH_2-phenyl	H	C(O)NH-(2*R*,3*S*)-2-$CO_2CH_2CH_3$-bicyclo[2.2.1]hept-5-en-3-yl
322	phenyl	5-$CO_2CH_2CH_3$	C(O)NH-1,3,3-$(CH_3)_3$-bicyclo[2.2.1]hept-2-yl
323	phenyl	5-$CO_2CH_2CH_3$	C(O)NHCH_2-adamantan-1-yl
324	phenyl	5-$CO_2CH_2CH_3$	C(O)NH-adamantan-2-yl
325	phenyl	5-$CO_2CH_2CH_3$	C(O)NHCH(CH_3)-adamantan-1-yl

and pharmaceutically acceptable forms thereof.

An example of the present invention is a compound of Formula (Ic)



Formula (Ic)

wherein X_1R_1, X_3R_3 and R_4 are dependently selected from

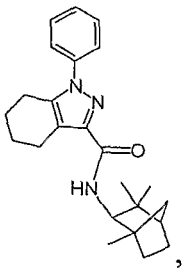
Cpd	X_1R_1	R_4	X_3R_3
290	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NH-piperidin-1-yl
291	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NH-morpholin-4-yl
292	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NH-(1*S*,2*R*,4*R*)-1-CH_3-3,3-$(CH_3)_2$-bicyclo[2.2.1]hept-2-yl
293	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NH-(*R*-CH)(CH_3)-cyclohexyl
294	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NH-(*S*-CH)(CH_3)-phenyl
295	(2,4-Cl_2)phenyl	CH-(4-F)phenyl	C(O)NH-(*R*-CH)(CH_3)-cyclohexyl
296	(2,4-Cl_2)phenyl	CH-(4-F)phenyl	C(O)NH-(*R*-CH)(CH_3)-phenyl
297	(2,4-Cl_2)phenyl	CH-(4-F)phenyl	C(O)NH-piperidin-1-yl
298	(2,4-Cl_2)phenyl	CH-(4-F)phenyl	C(O)NH-morpholin-4-yl
307	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NH-(*R*-CH)(CH_3)-phenyl
308	(2,4-Cl_2)phenyl	CH-(4-F)phenyl	C(O)NH-(*S*-CH)(CH_3)-phenyl
309	(2,4-Cl_2)phenyl	CH-(4-F)phenyl	C(O)NH-(*S*-CH)(CH_3)-cyclohexyl
310	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NHNH-(4-SO_2NH_2)phenyl
311	(2,4-Cl_2)phenyl	CH-(4-F)phenyl	C(O)NHNH-pyridin-4-yl
319	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NHCH_2-pyridin-2-yl
320	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NHCH(CH_3)-pyridin-2-yl
321	(2,4-Cl_2)phenyl	CH-(4-Cl)phenyl	C(O)NH-(*S*-CH)(CH_3)-cyclohexyl
339	(2,4-Cl_2)phenyl	CH-(4-F)phenyl	C(O)NH-azepan-1-yl
340	(2,4-Cl_2)phenyl	CH-thien-2-yl	C(O)NH-CH(*R*-CH_3)-phenyl
341	(2,4-Cl_2)phenyl	CH-thien-2-yl	C(O)NH-CH(*R*-CH_3)-cyclohexyl
342	(2,4-Cl_2)phenyl	CH-thien-2-yl	C(O)NH-piperidin-1-yl
343	(2,4-Cl_2)phenyl	CH-thien-2-yl	C(O)NH-azepan-1-yl
344	(2,4-Cl_2)phenyl	CH-thien-2-yl	C(O)NH-2,6-$(CH_3)_2$-piperidin-1-yl
345	(2,4-Cl_2)phenyl	CH-thien-2-yl	C(O)NH-pyrrolidin-1-yl
346	(2,4-Cl_2)phenyl	CH-thien-2-yl	C(O)NH-hexahydro-cyclopenta[c]pyrrol-2-yl
347	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-piperidin-1-yl
348	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-azepan-1-yl
349	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-2,6-$(CH_3)_2$-piperidin-1-yl

Cpd	X_1R_1	R_4	X_3R_3
350	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-hexahydro-cyclopenta[c]pyrrol-2-yl
351	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-CH(*R*-CH_3)-cyclohexyl
352	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-CH(*S*-CH_3)-cyclohexyl
353	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-CH(*R*-CH_3)-phenyl
354	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-CH(*S*-CH_3)-phenyl
355	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-(*R*-CH)(CH_2OH)-phenyl
356	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-(*S*-CH)(CH_2OH)-phenyl
357	(2,4-Cl_2)phenyl	CH-thien-3-yl	C(O)NH-pyrrolidin-1-yl
358	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-CH(*R*-CH_3)-phenyl
359	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-CH(*S*-CH_3)-phenyl
360	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-CH(*R*-CH_3)-cyclohexyl
361	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-CH(*S*-CH_3)-cyclohexyl
362	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-2,6-$(CH_3)_2$-piperidin-1-yl
363	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-azepan-1-yl
364	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-piperidin-1-yl
365	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-hexahydro-cyclopenta[c]pyrrol-2-yl
366	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-(*R*-CH)(CH_2OH)-phenyl
367	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-(*S*-CH)(CH_2OH)-phenyl
368	(2,4-Cl_2)phenyl	CH-fur-3-yl	C(O)NH-pyrrolidin-1-yl
369	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-CH(*R*-CH_3)-cyclohexyl
370	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-CH(*S*-CH_3)-cyclohexyl
371	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-CH(*R*-CH_3)-phenyl
372	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-CH(*S*-CH_3)-phenyl
373	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-azepan-1-yl
374	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-piperidin-1-yl
375	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-2,6-$(CH_3)_2$-piperidin-1-yl
376	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-hexahydro-cyclopenta[c]pyrrol-2-yl
377	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-pyrrolidin-1-yl
378	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-(*R*-CH)(CH_2OH)-phenyl
379	(2,4-Cl_2)phenyl	CH-fur-2-yl	C(O)NH-(*S*-CH)(CH_2OH)-phenyl
380	(2,4-Cl_2)phenyl	CH-(4-Br)phenyl	C(O)NH-hexahydro-cyclopenta[c]pyrrol-2-yl
381	(2,4-Cl_2)phenyl	CH-(4-Br)phenyl	C(O)NH-(*R*-CH)(CH_3)-pyridin-2-yl
382	(2,4-Cl_2)phenyl	CH-(4-Br)phenyl	C(O)NH-(*R*-CH)(CH_3)-cyclohexyl
383	(2,4-Cl_2)phenyl	CH-(4-Br)phenyl	C(O)NH-(*R*-CH)(CH_3)-phenyl
384	(2,4-Cl_2)phenyl	CH-(4-Br)phenyl	C(O)NH-piperidin-1-yl
385	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-CH(*R*-CH_3)-cyclohexyl
386	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-CH(*R*-CH_3)-phenyl
387	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-piperidin-1-yl

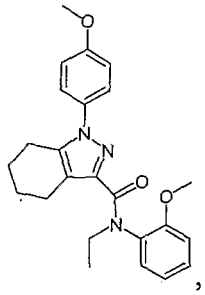
Cpd	X_1R_1	R_4	X_3R_3
388	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-azepan-1-yl
389	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-2,6-$(CH_3)_2$-piperidin-1-yl
390	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-hexahydro-cyclopenta[c]pyrrol-2-yl
391	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-CH(*S*-CH_3)-cyclohexyl
392	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-CH(*S*-CH_3)-phenyl
393	(2,4-Cl_2)phenyl	CH-(5-Cl)thien-2-yl	C(O)NH-pyrrolidin-1-yl
394	(2,4-Cl_2)phenyl	CH-(5-Br)thien-2-yl	C(O)NH-piperidin-1-yl
395	(2,4-Cl_2)phenyl	CH-(5-Br)thien-2-yl	C(O)NH-azepan-1-yl
396	(2,4-Cl_2)phenyl	CH-(5-Br)fur-2-yl	C(O)NH-hexahydro-cyclopenta[c]pyrrol-2-yl
397	(2,4-Cl_2)phenyl	CH-(5-Br)fur-2-yl	C(O)NH-CH(*R*-CH_3)-phenyl
398	(2,4-Cl_2)phenyl	CH-(5-Br)fur-2-yl	C(O)NH-CH(*R*-CH_3)-cyclohexyl
399	(2,4-Cl_2)phenyl	CH-(3-Br)thien-2-yl	C(O)NH-2,6-$(CH_3)_2$-piperidin-1-yl
400	(2,4-Cl_2)phenyl	CH-(4-Br)thien-3-yl	C(O)NH-piperidin-1-yl

and pharmaceutically acceptable forms thereof.

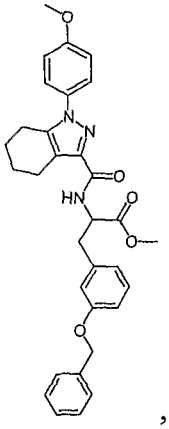
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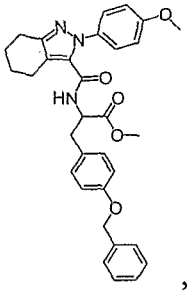
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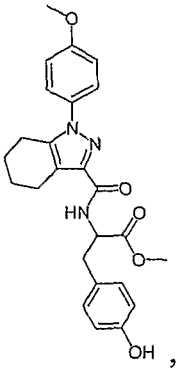
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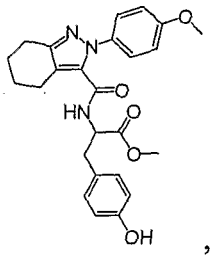
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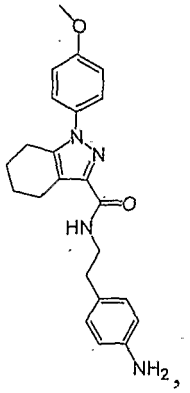
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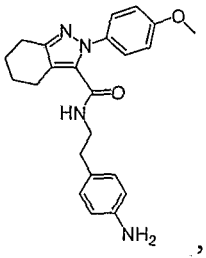
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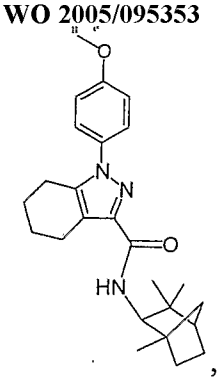
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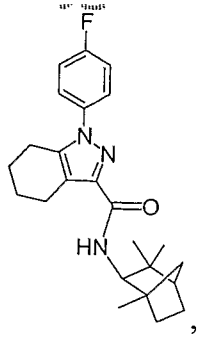
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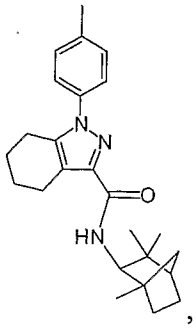
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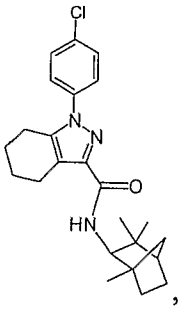
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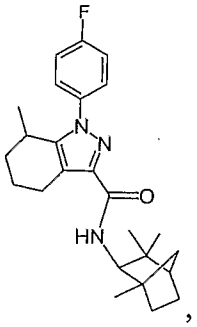
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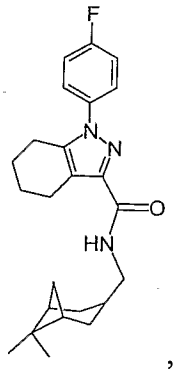
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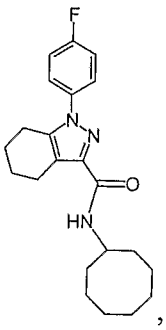
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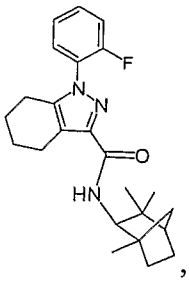
13 MS 410 MH^+



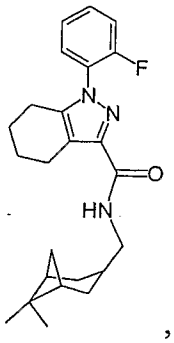
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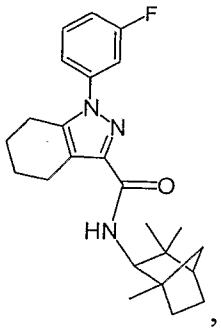
15 MS 370 MH^+



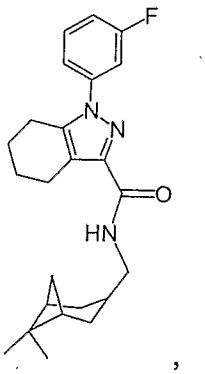
16 MS 396 MH^+



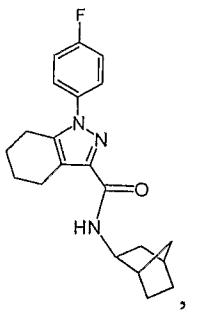
17 MS 396 MH^+



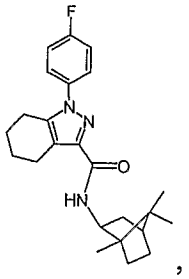
18 MS 396 MH^+



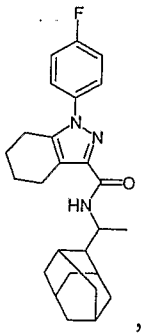
19 MS 396 MH^+



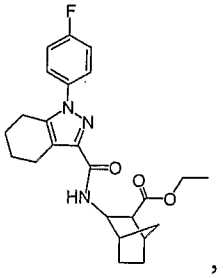
20 MS 354 MH^+



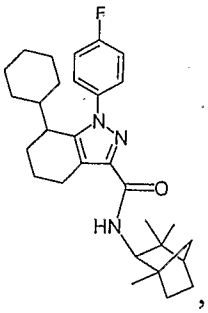
21 MS 396 MH^+



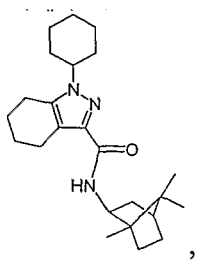
22 MS 422 MH^+



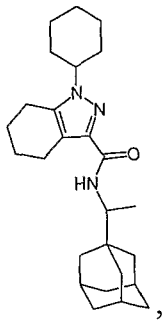
23 MS 426.2 MH^+



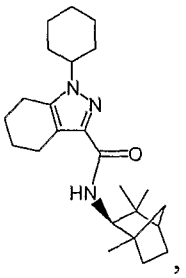
24 MS 478 MH^+



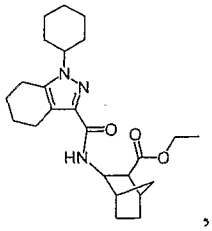
25 MS 384.1 MH^+



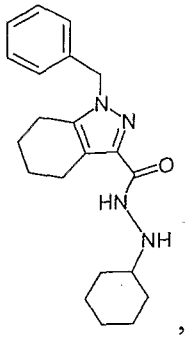
26 MS 410.1 MH^+



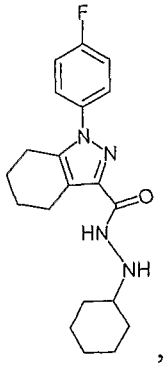
27 MS 384.1 MH^+



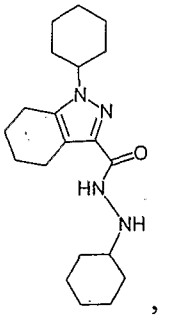
28 MS 414.1 MH^+



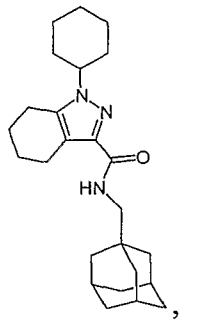
29 MS 352.9 MH^+



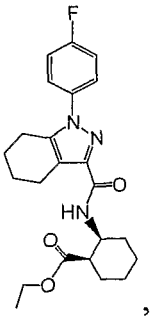
30 MS 357 MH^+



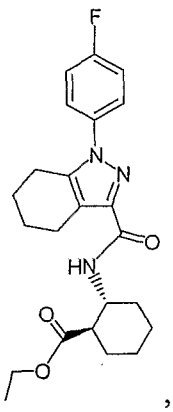
31 MS 345.1 MH^+



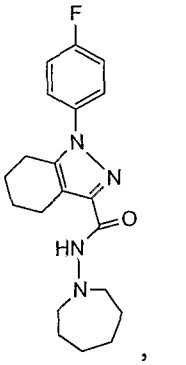
32 MS 396.1 MH^+



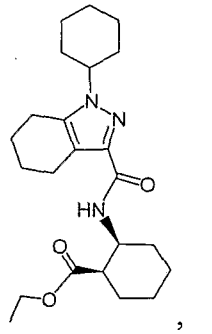
33 MS 414.2 MH^+



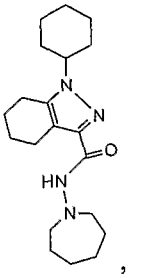
34 MS 414 MH^+



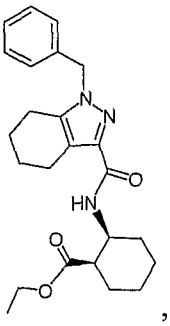
35 MS 357.2 MH^+



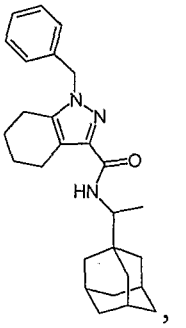
36 MS 402.1 MH^+



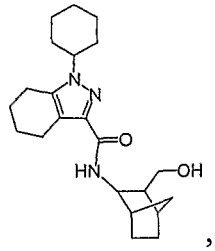
37 MS 345.1 MH^+



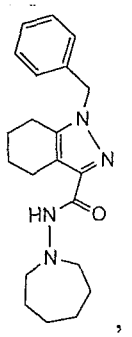
38 MS 410 MH^+



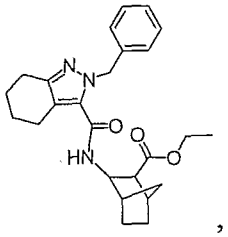
39 MS 418 MH^+



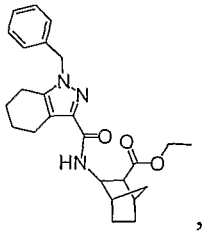
40 MS 372.1 MH^+



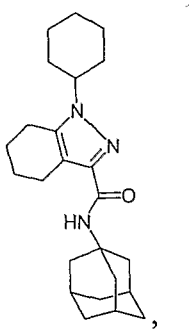
41 MS 353 MH^+



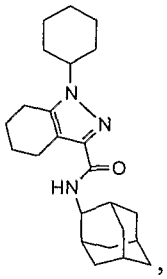
42 MS 422 MH^+



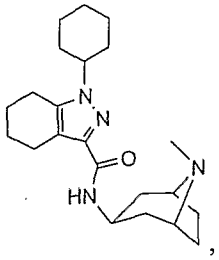
43 MS 422 MH^+



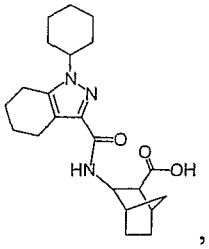
44 MS 382.1 MH^+



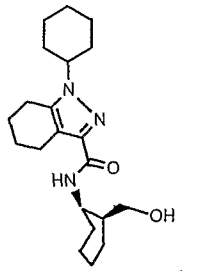
45 MS 382.1 MH^+



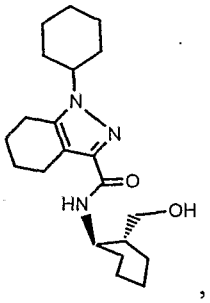
46 MS 371 MH^+



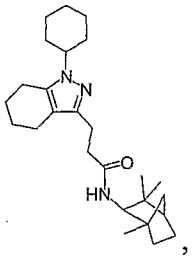
47 MS 386 MH^+



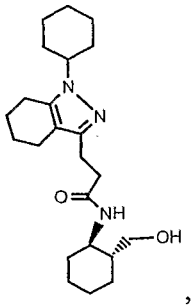
48 MS 360.1 MH^+



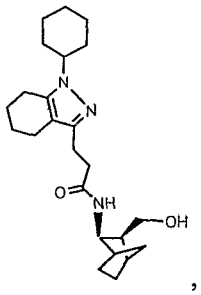
49 MS 360.1 MH^+



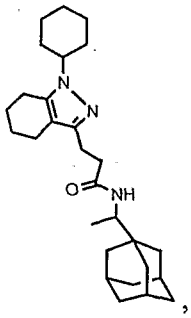
50 Example 15



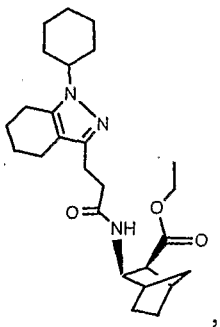
51 MS 388.1 MH^+



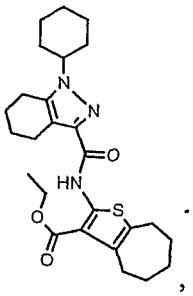
52 MS 400 MH^+



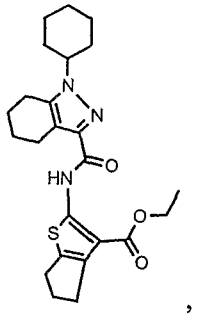
53 MS 442.1 MH^+



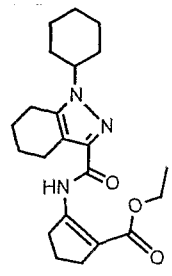
54 MS 442 MH^+



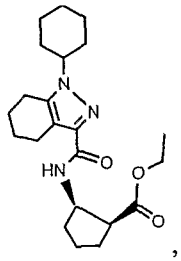
55 MS 470 MH^+



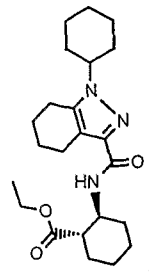
56 MS 442 MH^+



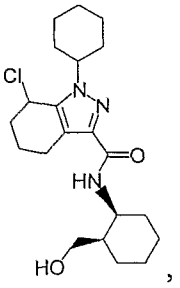
57 MS 386 MH^+



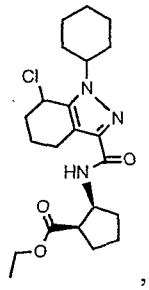
58 MS 388 MH^+



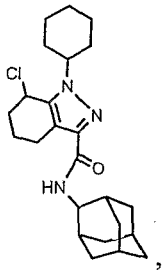
59 MS 402.1 MH^+



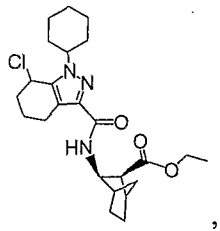
60 Example 23



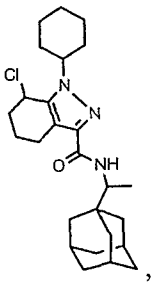
61 MS 422 MH^+



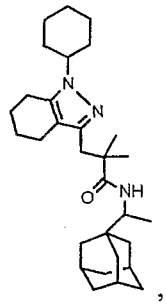
62 MS 416 MH^+



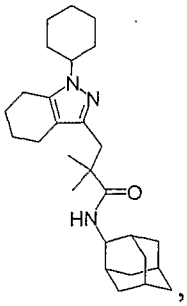
63 MS 448 MH^+



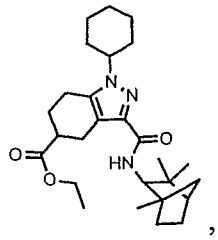
64 MS 444.1 MH^+



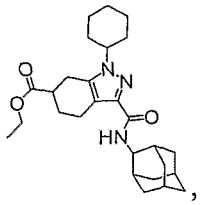
65 MS 466.1 MH^+



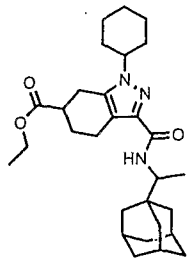
66 Example 16



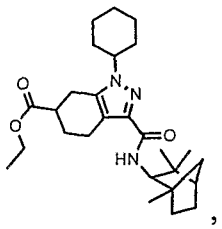
67 MS 456 MH^+



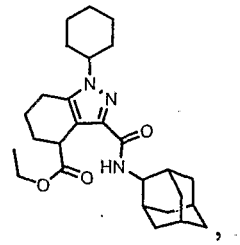
68 MS 454 MH^+



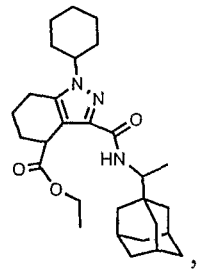
69 MS 482 MH^+



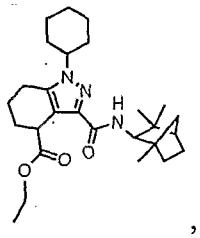
70 MS 456 MH^+

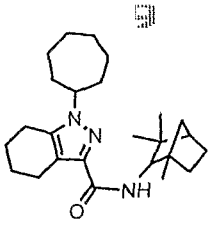


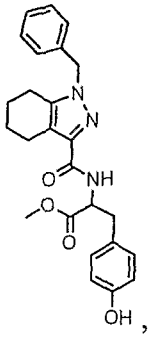
71 MS 454 MH^+

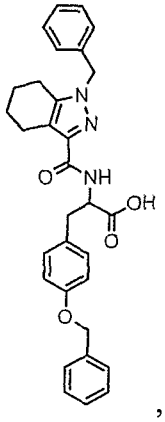


72 MS 482 MH^+

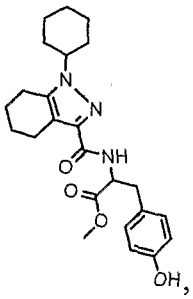


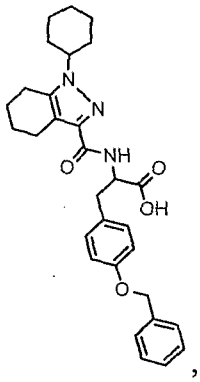


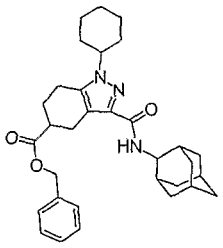


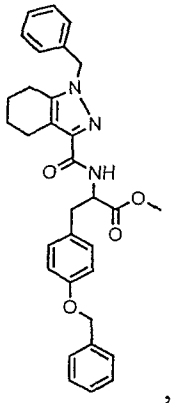


73 MS 456 MH^+ **74** MS 398 MH^+ **75** MS 434.2 MH^+ **76** MS 510.2 MH^+

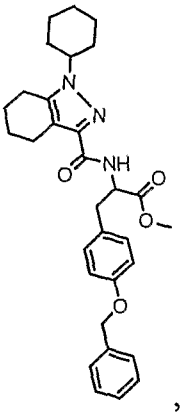


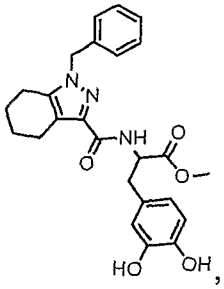


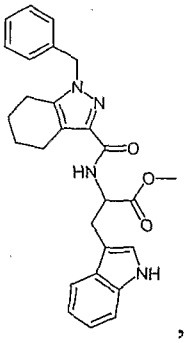


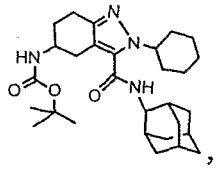


77 MS 426.2 MH^+ **78** MS 502.3 MH^+ **79** MS 516 MH^+ **80** MS 524.2 MH^+

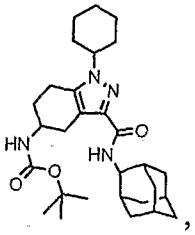


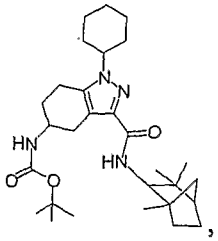


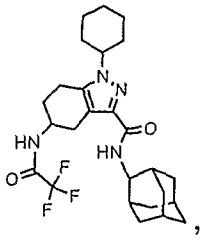


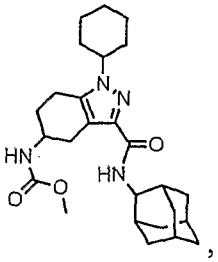


81 MS 516.3 MH^+ **82** MS 450 MH^+ **83** MS 457 MH^+ **84** MS 497 MH^+

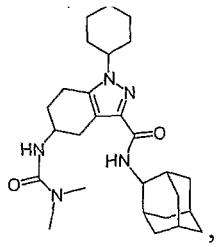




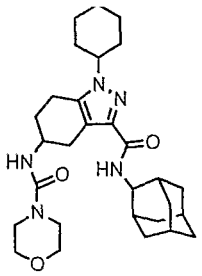




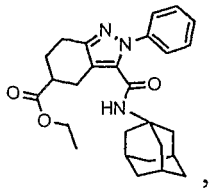
85 MS 497 MH^+ **86** Example 8 **87** MS 493 MH^+ **88** MS 455 MH^+



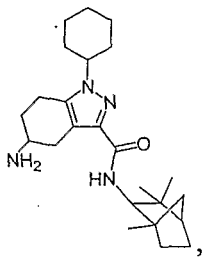
89 Example 9



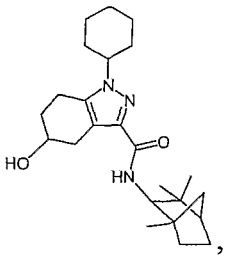
90 MS 510 MH^+



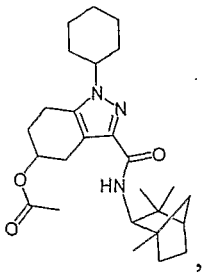
91 MS 448 MH^+



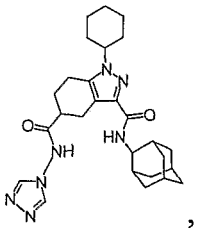
92 Example 8



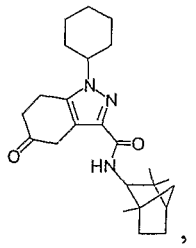
93 Example 8



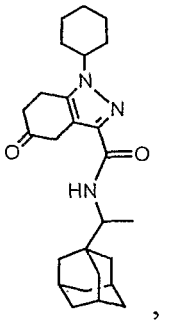
94 MS 442 MH^+



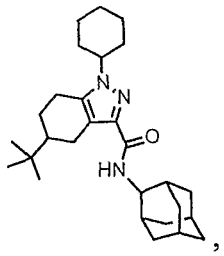
95 MS 492 MH^+



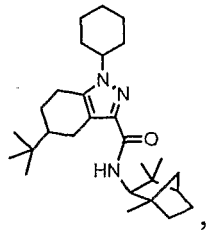
96 Example 22



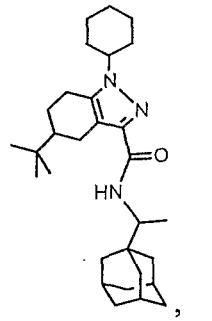
97 MS 422.2 MH^+



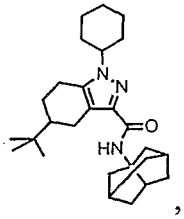
98 MS 438 MH^+



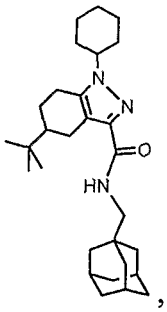
99 MS 440 MH^+



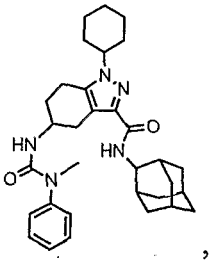
100 MS 466 MH^+



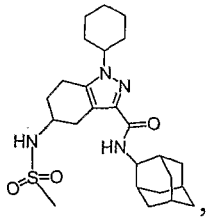
101 MS 424 MH^+



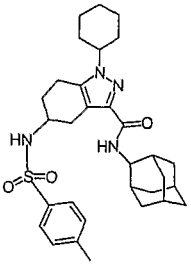
102 MS 452 MH^+



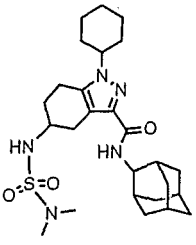
103 MS 530 MH^+



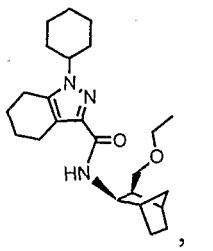
104 MS 475 MH^+



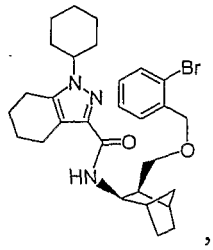
1056 MS 551 MH^+



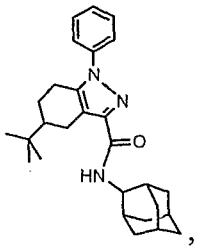
106 MS 504 MH^+



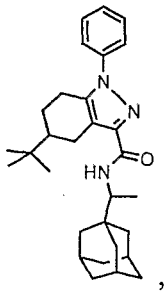
107 MS 400.3 MH^+



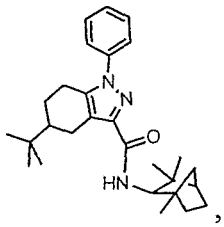
108 MS 542.2 MH^+



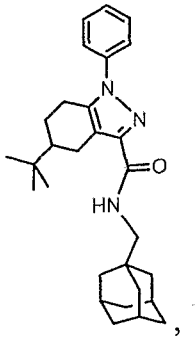
109 MS 432 MH^+



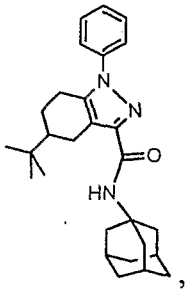
110 MS 460 MH^+



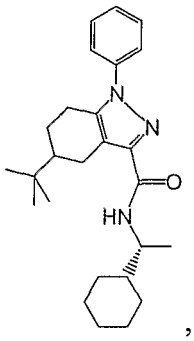
111 MS 434 MH^+



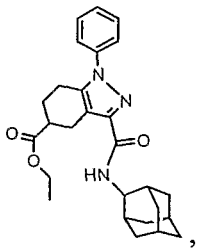
112 MS 446 MH^+



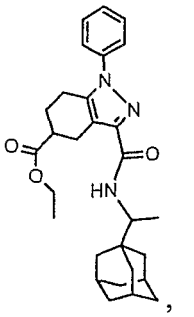
113 MS 432 MH^+



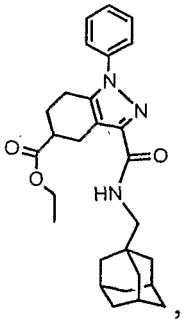
114 MS 408 MH^+



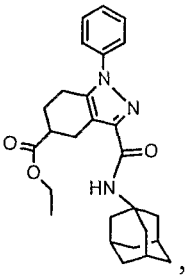
115 MS 448 MH^+



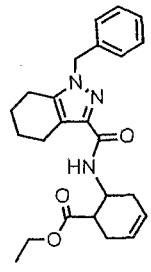
116 MS 476 MH^+



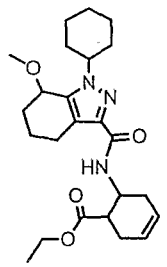
117 MS 462 MH^+



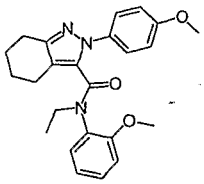
118 MS 448 MH^+



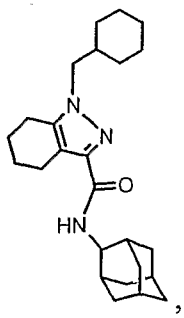
119 MS 408.1 MH^+



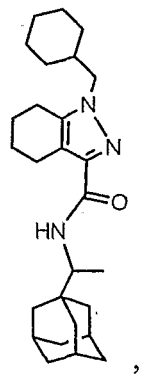
120 MS 430.1 MH^+



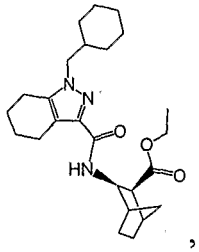
121 MS 406 MH^+



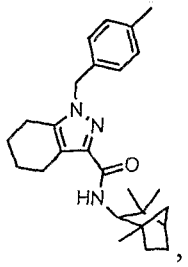
122 MS 396 MH^+



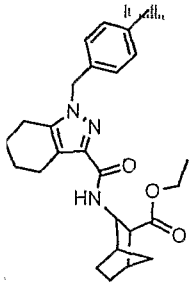
123 MS 424 MH^+



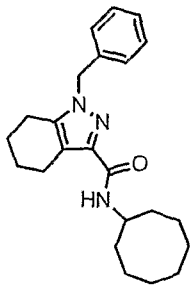
124 MS 428 MH^+



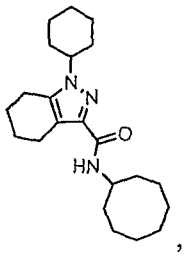
125 MS 406 MH^+



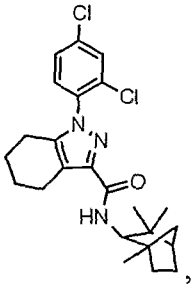
126 MS 436 MH^+



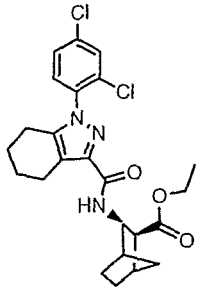
127 MS 366 MH^+



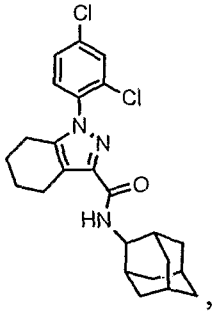
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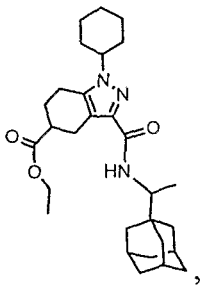
129 MS 446 MH^+



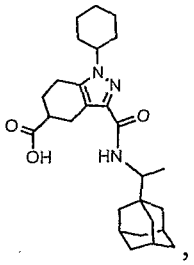
130 MS 476 MH^+



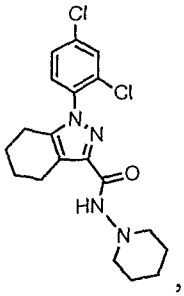
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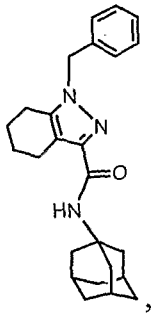
132 MS 482 MH^+



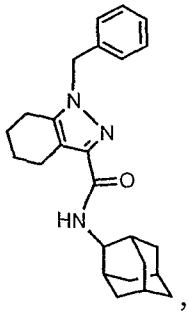
133 MS 454 MH^+



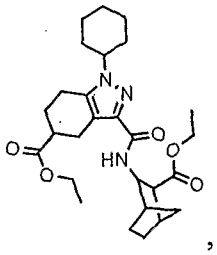
134 MS 407 MH^+



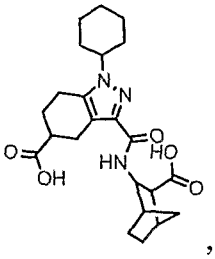
135 MS 404.2 MH^+



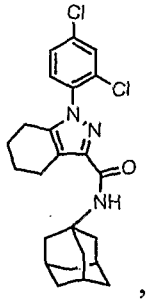
136 MS 390 MH^+



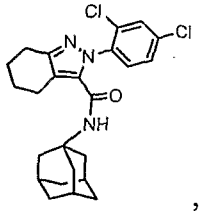
137 MS 486 MH^+



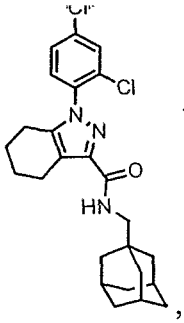
138 MS 430 MH^+



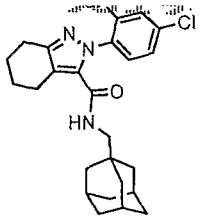
139 MS 444.1 MH^+



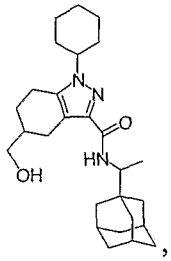
140 MS 444.1 MH^+



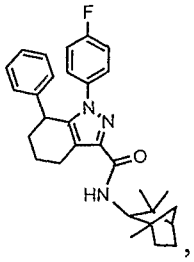
141 MS 458 MH^+



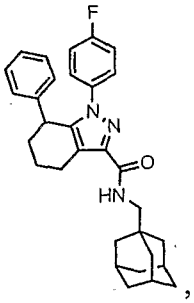
142 MS 458.1 MH^+



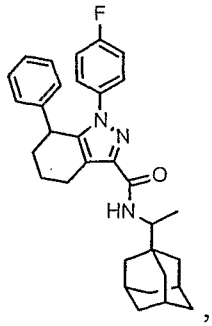
143 Example 19



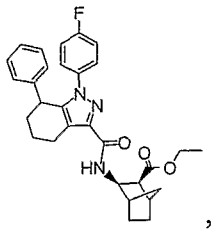
144 MS 472.1 MH^+



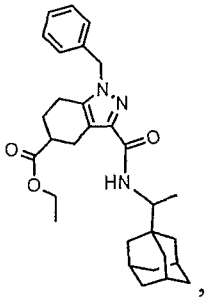
145 MS 484.1 MH^+



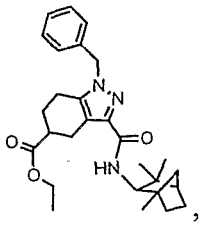
146 MS 498.2 MH^+



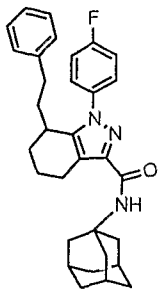
147 MS 502.1 MH^+



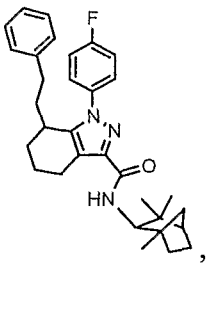
148 MS 490 MH^+



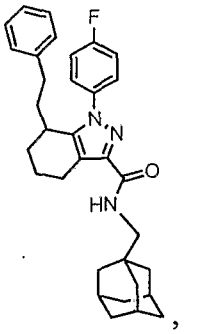
149 MS 464 MH^+



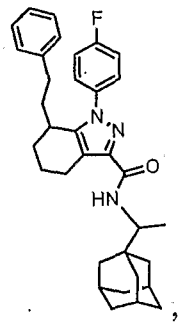
150 MS 498.2 MH^+



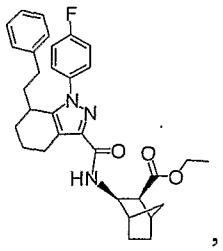
151 MS 500.2 MH^+



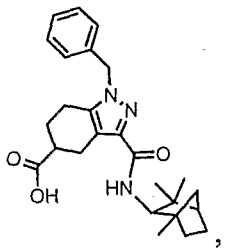
152 MS 512.2 MH^+



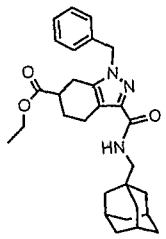
153 MS 526.3 MH^+



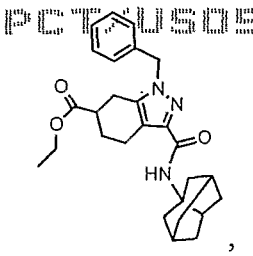
154 MS 530.2 MH^+



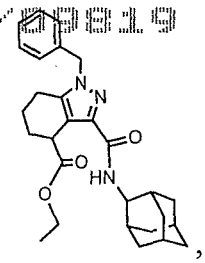
155 MS 436 MH^+



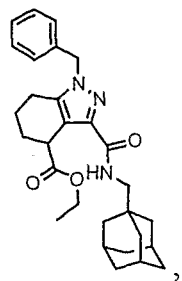
156 MS 476 MH^+



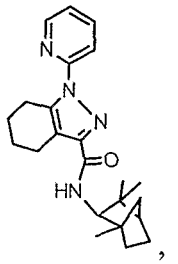
157 MS 448 MH^+



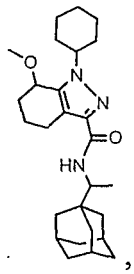
158 MS 462.3 MH^+



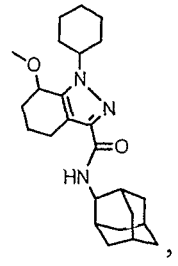
159 MS 476 MH^+



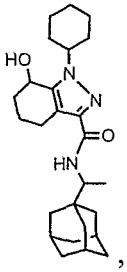
160 MS 379 MH^+



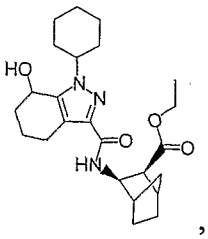
161 MS 440 MH^+



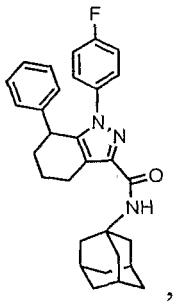
162 MS 412 MH^+



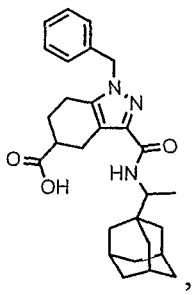
163 MS 425.8 MH^+



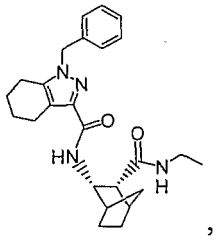
164 Example 24



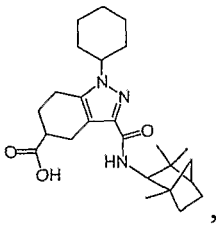
165 MS 470.2 MH^+



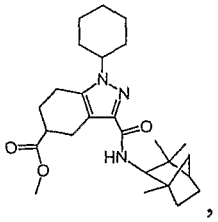
166 MS 462 MH^+



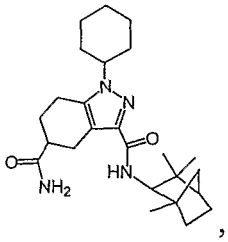
167 MS 421 MH^+



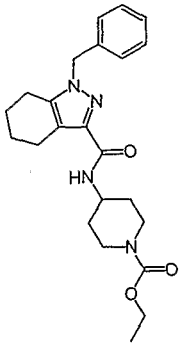
168 MS 428 MH^+



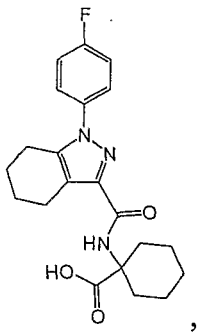
169 MS 442 MH^+



170 MS 427 MH^+

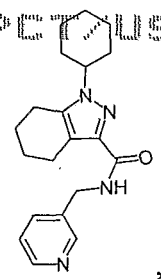


171 MS 411 MH^+

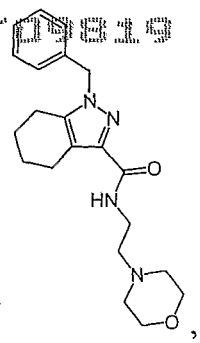


172 MS 386.2 MH^+

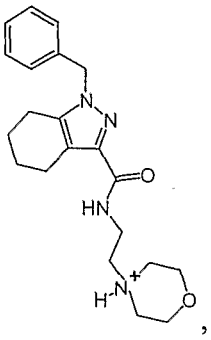
PCT/US05/09819



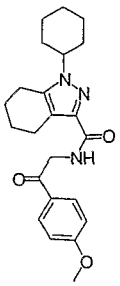
173 MS 339 MH^+



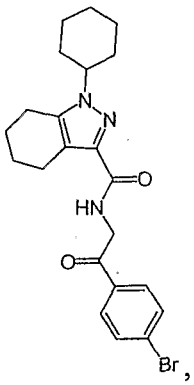
174 MS 369 MH^+



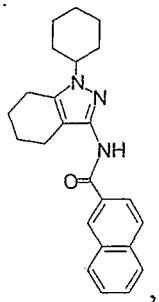
175 MS 370 MH^+



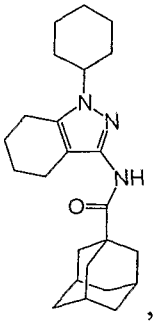
176 Example 4



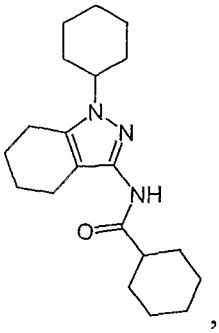
177 MS 445 MH^+



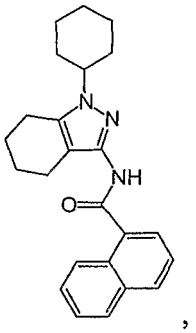
178 Example 6



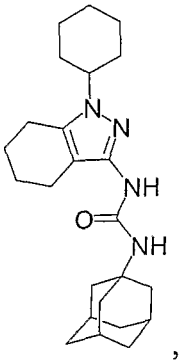
179 MS 382 MH^+



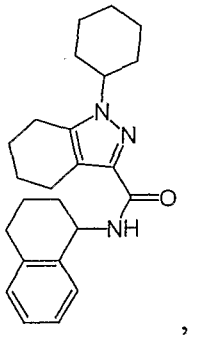
180 MS 330 MH^+



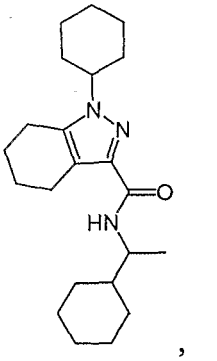
181 MS 374 MH^+



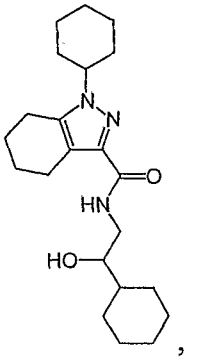
182 Example 27



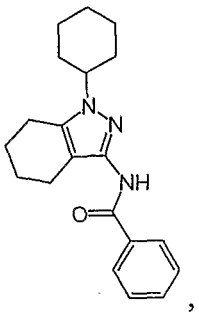
183 MS 378 MH^+



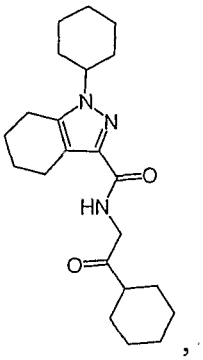
184 MS 358 MH^+



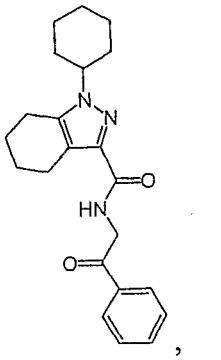
185 MS 374 MH^+



186 MS 324 MH^+

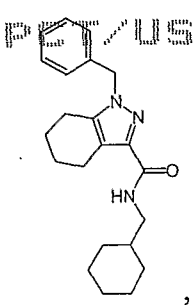


187 MS 372 MH^+

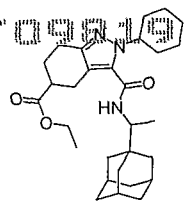


188 MS 366 MH^+

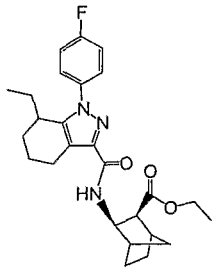
PCT/US05/09819



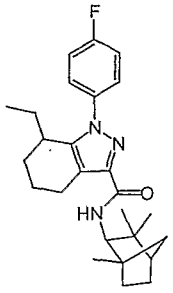
189 MS 352 MH^+



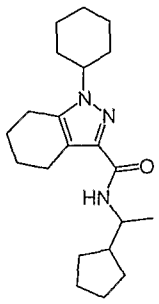
190 MS 482 MH^+



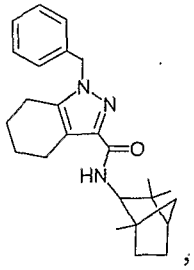
191 MS 454 MH^+



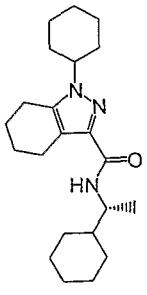
192 MS 424 MH^+



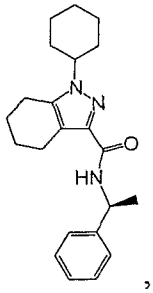
193 MS 344 MH^+



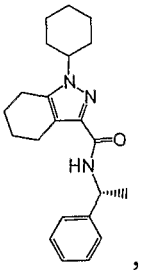
194 Example 2



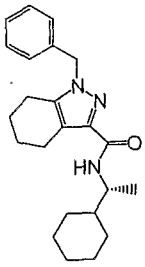
195 MS 358 MH^+



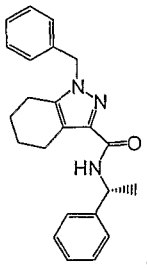
196 MS 352 MH^+



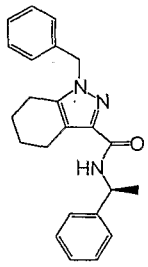
197 MS 352 MH^+



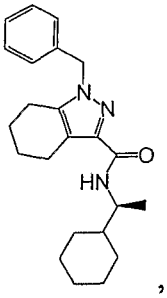
198 MS 366 MH^+



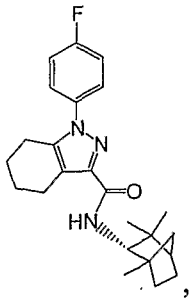
199 MS 360 MH^+



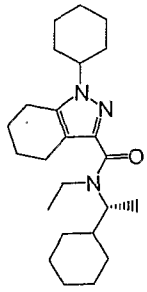
200 MS 360 MH^+



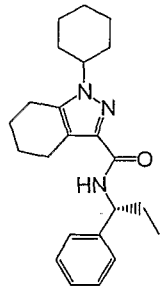
201 MS 366 MH^+



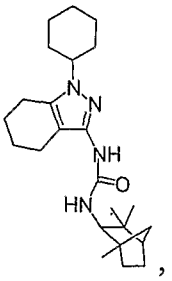
202 MS 396 MH^+



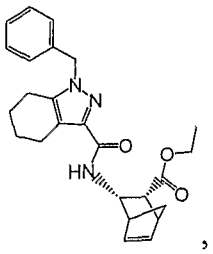
203 MS 386 MH^+



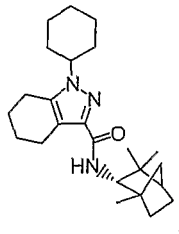
204 MS 366 MH^+



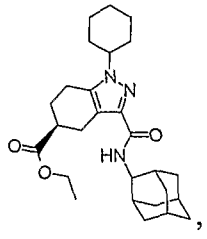
205 MS 399 MH^+



206 MS 420.1 MH^+

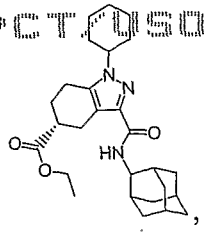


207 MS 384.1 MH^+

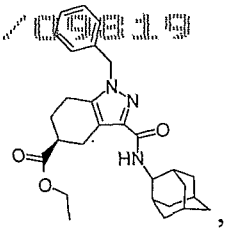


208 Example 1

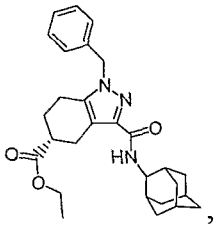
PCT/US2005/009819



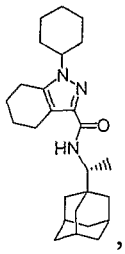
209 Example 1



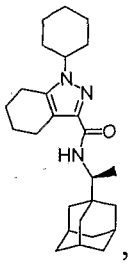
210 MS 462 MH^+



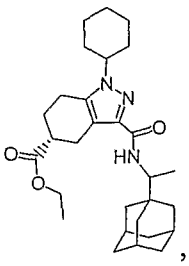
211 MS 462 MH^+



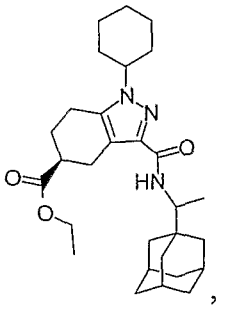
212 MS 410 MH^+



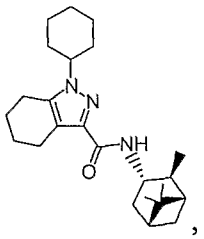
213 MS 410 MH^+



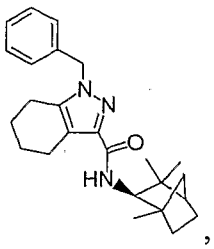
214 MS 482 MH^+



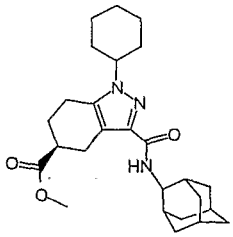
215 MS 482 MH^+



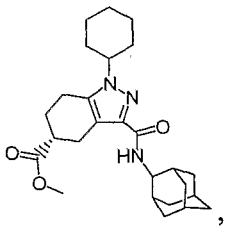
216 MS 384 MH^+



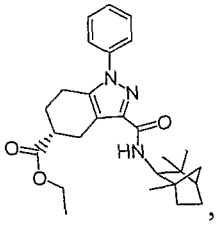
217 MS 392 MH^+



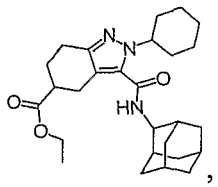
218 MS 440 MH^+



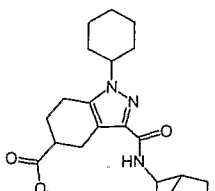
219 MS 440 MH^+



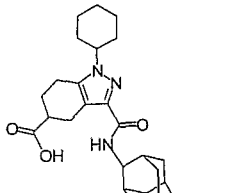
220 MS 450 MH^+



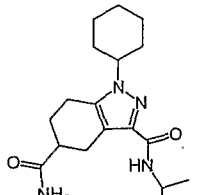
221 MS 454 MH^+



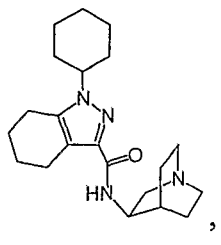
222 MS 454 MH^+



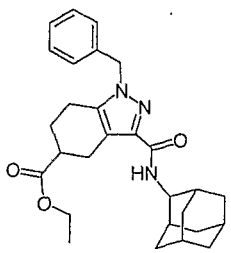
223 Example 7



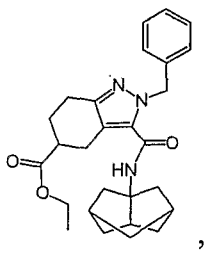
224 MS 453 MH^+



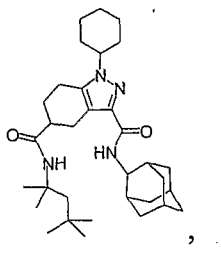
225 MS 357 MH^+



226 MS 462 MH^+

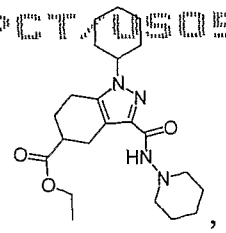


227 MS 448 MH^+

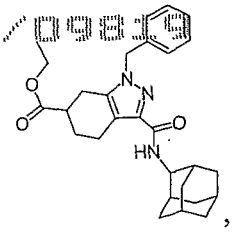


228 Example 7

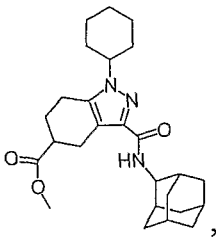
PCT/US05/09819



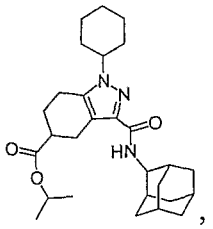
229 MS 403 MH^+



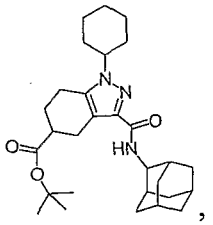
230 MS 462 MH^+



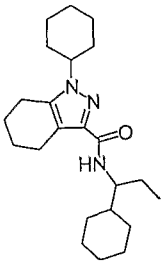
231 MS 440 MH^+



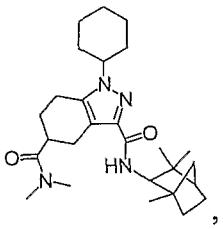
232 MS 468 MH^+



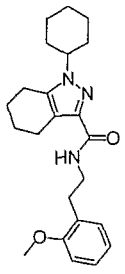
233 MS 482 MH^+



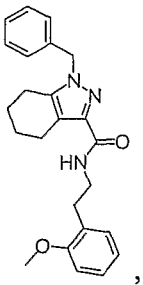
234 MS 372 MH^+



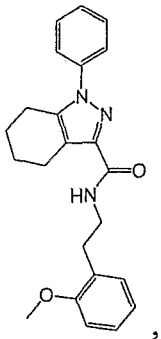
235 MS 455 MH^+



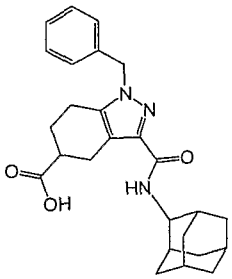
236 MS 382 MH^+



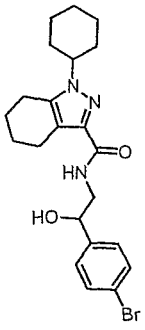
237 MS 390 MH^+



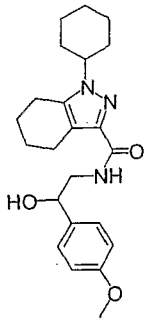
238 MS 376 MH^+



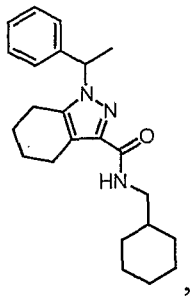
239 MS 434 MH^+



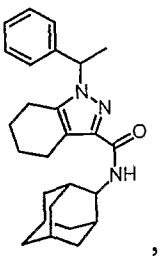
240 MS 447 MH^+



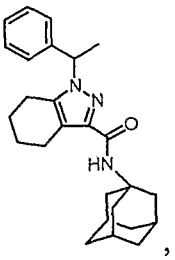
241 Example 4



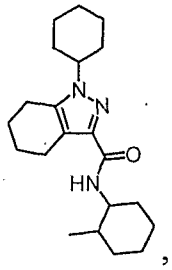
242 MS 366 MH^+



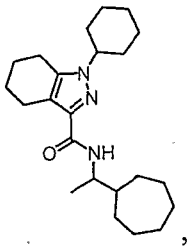
243 MS 404 MH^+



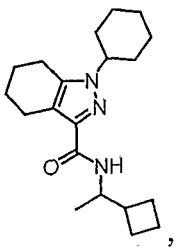
244 MS 404 MH^+



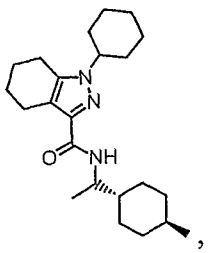
245 MS 344 MH^+



246 MS 372 MH^+

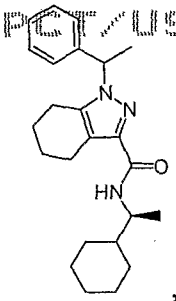


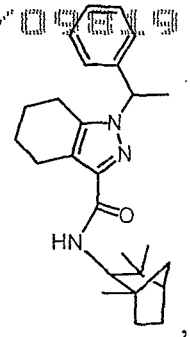
247 MS 330 MH^+



248 MS 372 MH^+

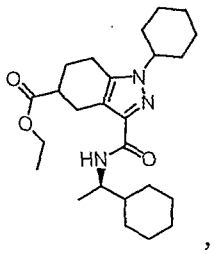
PCT/US05/09819



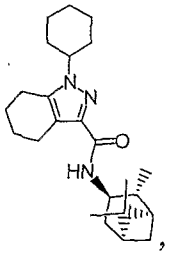


249 Example 3

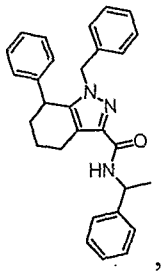
250 MS 406 MH^+



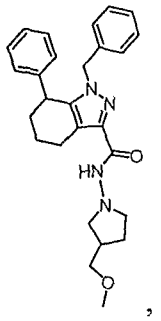
251 MS 430 MH^+



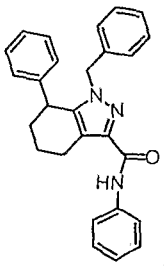
252 MS 384 MH^+



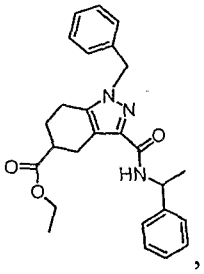
253 MS 436 MH^+



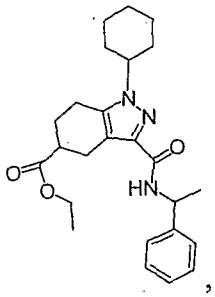
254 MS 445 MH^+



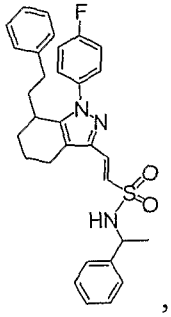
255 MS 408 MH^+



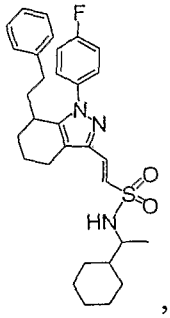
256 MS 432 MH^+



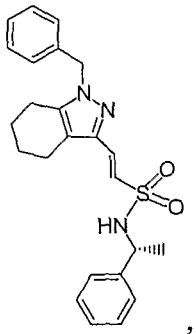
257 MS 424 MH^+



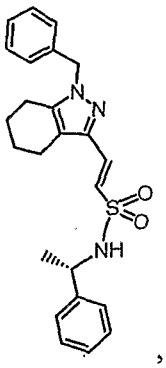
258 Example 20



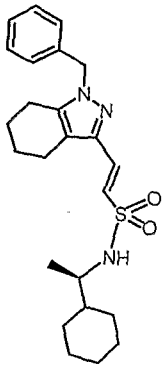
259 Example 20



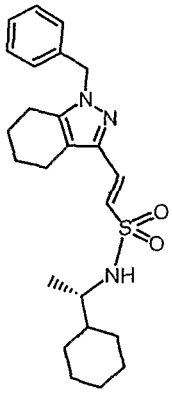
260 Example 11



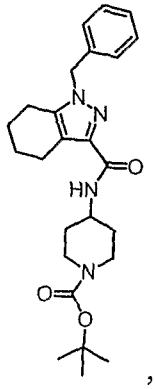
261 MS 422.1 MH^+



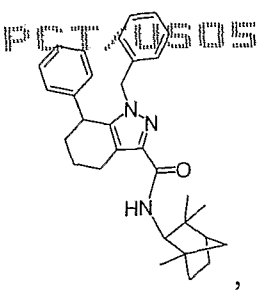
262 MS 428.2 MH^+



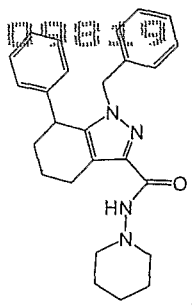
263 MS 428.1 MH^+



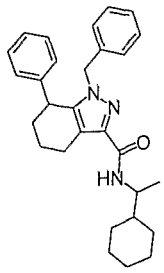
264 MS 439 MH^+



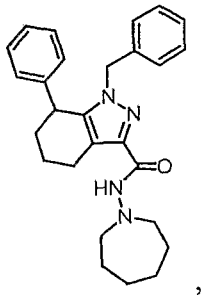
265 MS 468 MH^+



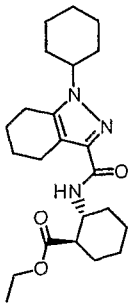
266 MS 415 MH^+



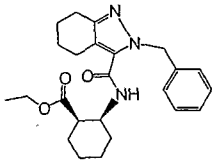
267 MS 442 MH^+



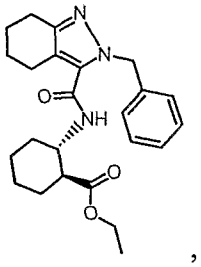
268 MS 429 MH^+



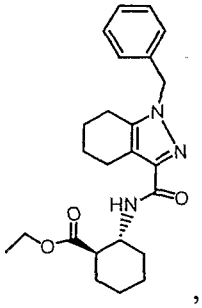
269 MS 402.1 MH^+



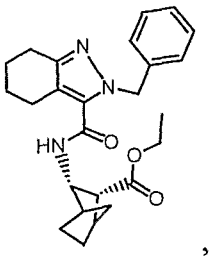
270 MS 410 MH^+



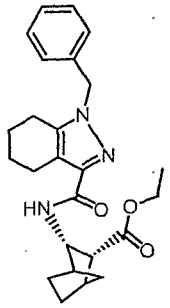
271 MS 410 MH^+



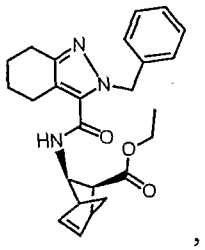
272 MS 410 MH^+



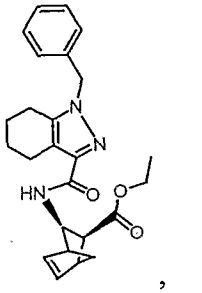
273 MS 422 MH^+



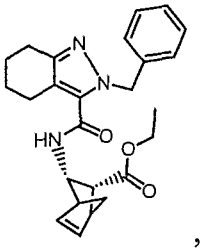
274 MS 422 MH^+



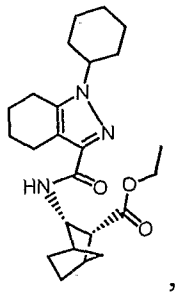
275 MS 420 MH^+



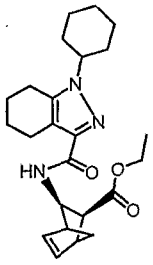
276 MS 420 MH^+



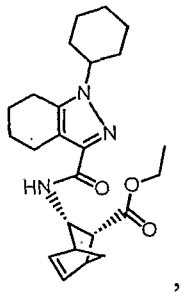
277 MS 420.1 MH^+



278 MS 414.2 MH^+

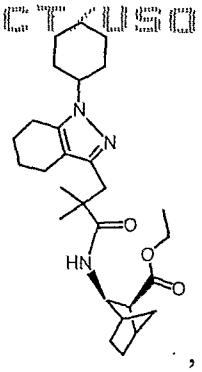


279 MS 412 MH^+

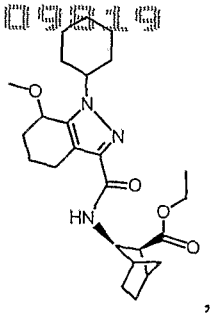


280 MS 412.1 MH^+

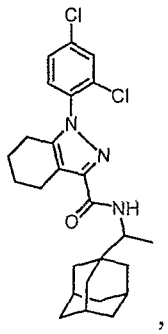
PCT/US05/09819



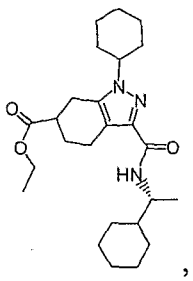
281 MS 470.1 MH^+



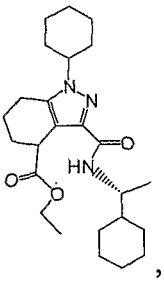
282 MS 444 MH^+



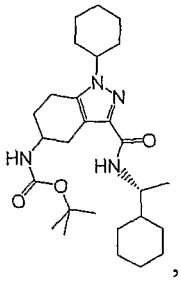
283 MS 472.1 MH^+



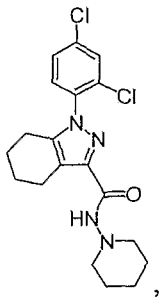
284 MS 430 MH^+



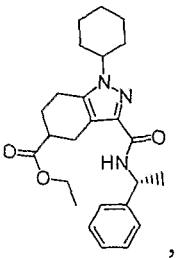
285 MS 430 MH^+



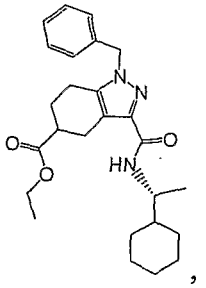
286 MS 473 MH^+



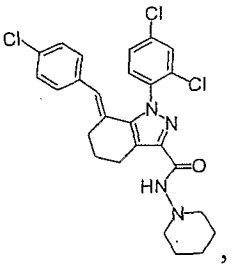
287 MS 393.1 MH^+



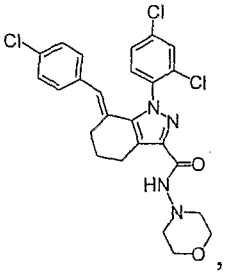
288 MS 424 MH^+



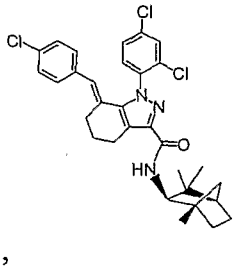
289 MS 438 MH^+



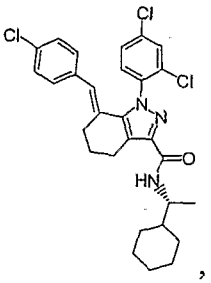
290 MS 515 MH^+



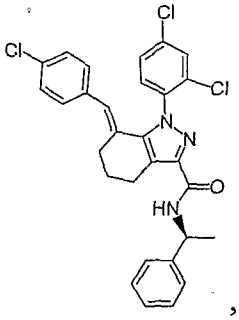
291 MS 517 MH^+



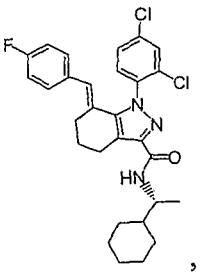
292 MS 568 MH^+



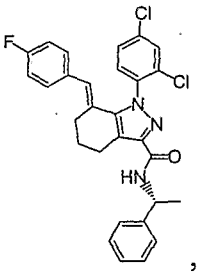
293 MS 542 MH^+



294 MS 536 MH^+

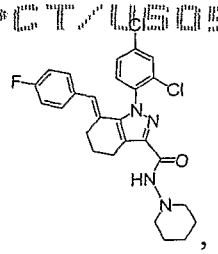


295 MS 526 MH^+

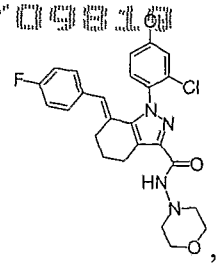


296 MS 520 MH^+

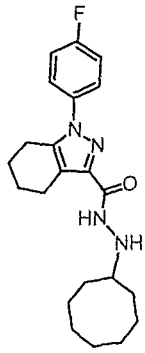
PCT/US05/09819



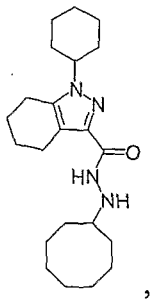
297 Example 10



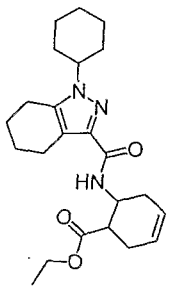
298 MS 501 MH^+



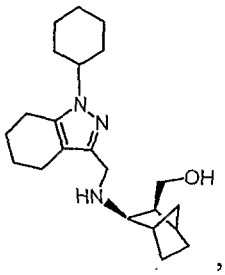
299 MS 385 MH^+



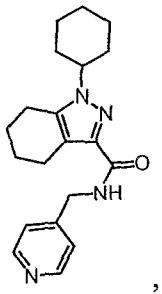
300 Example 21



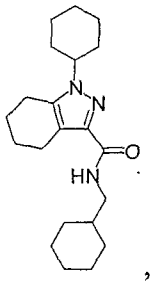
301 MS 400.1 MH^+



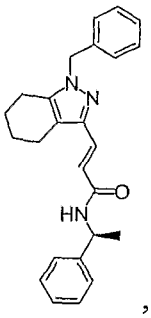
302 MS 358.1 MH^+



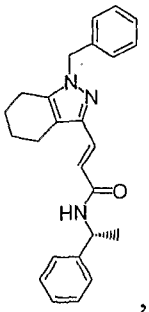
303 MS 339 MH^+



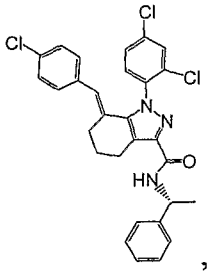
304 Example 5



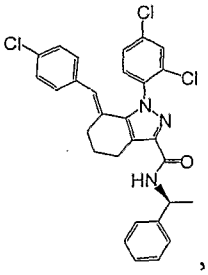
305 MS 386 MH^+



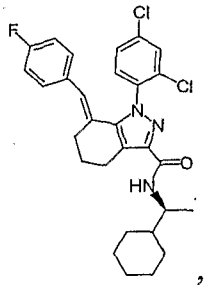
306 Example 12



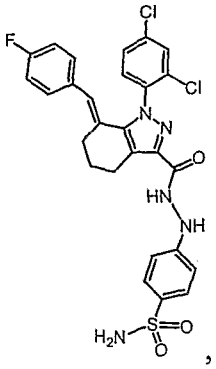
307 MS 536 MH^+



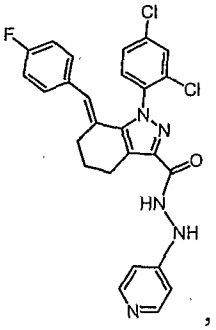
308 MS 520 MH^+



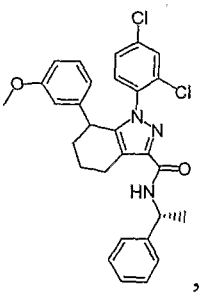
309 MS 526 MH^+



310 MS 586 MH^+

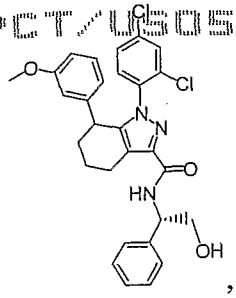


311 MS 508 MH^+

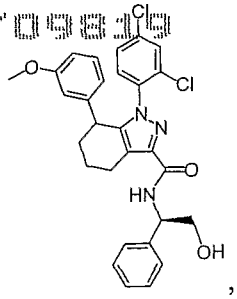


312 MS 520 MH^+

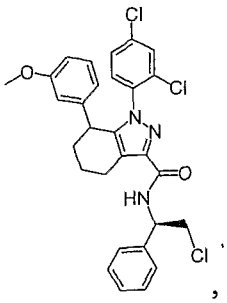
PCT/US05/09819



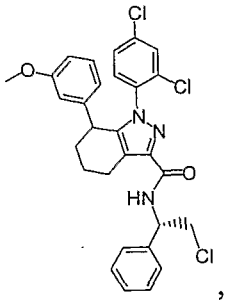
313 Example 25



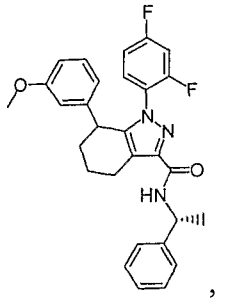
314 MS 536 MH^+



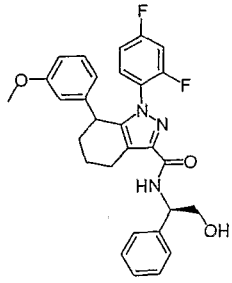
315 MS 556 MH^+



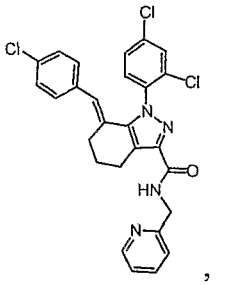
316 Example 26



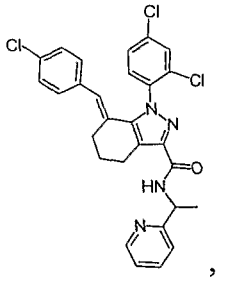
317 MS 488.2 MH^+



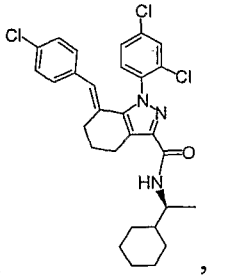
318 MS 504.1 MH^+



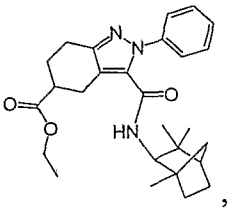
319 MS 523 MH^+



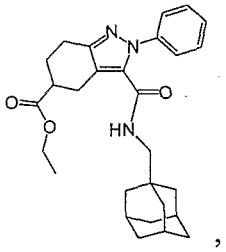
320 MS 537 MH^+



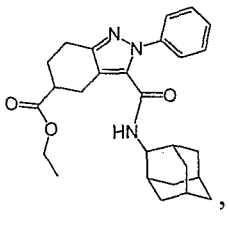
321 MS 542 MH^+



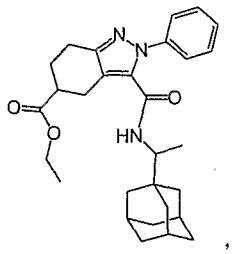
322 MS 450 MH^+



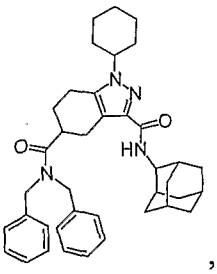
323 MS 462 MH^+



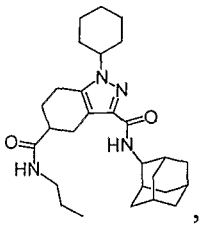
324 MS 448 MH^+



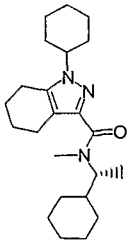
325 MS 476 MH^+



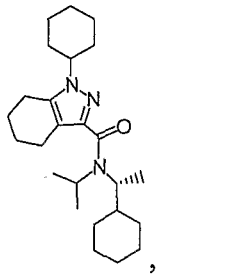
326 MS 505 MH^+



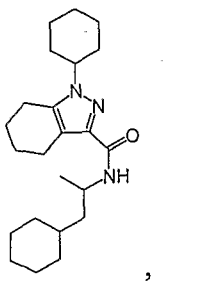
327 MS 467 MH^+



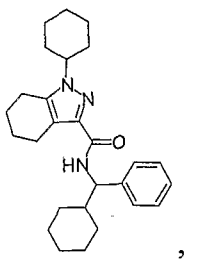
328 Example 17



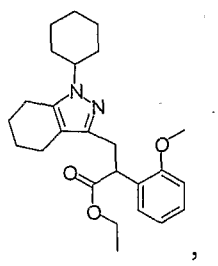
329 MS 400 MH^+



330 MS 372 MH^+

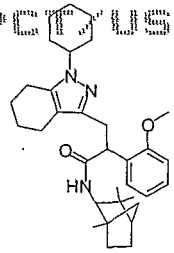


331 Example 18

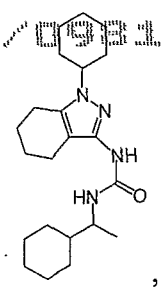


332 Example 13

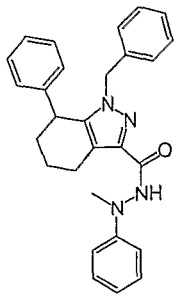
PCT/US05/09819



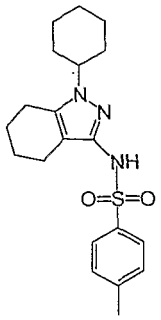
333 Example 14



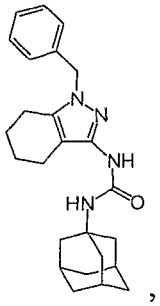
334 MS 373 MH^+



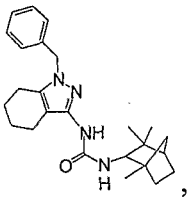
335 MS 459 MNa^+



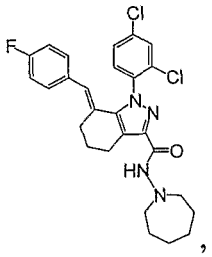
336 MS 374 MH^+



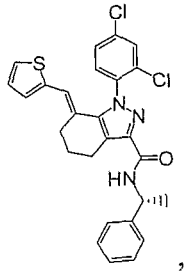
337 MS 405 MH^+



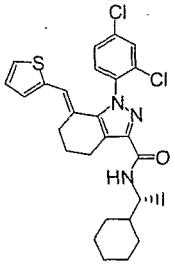
338 MS 407 MH^+



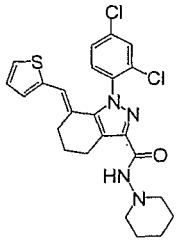
339 MS 513 MH^+



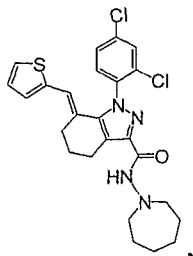
340 MS 508 MH^+



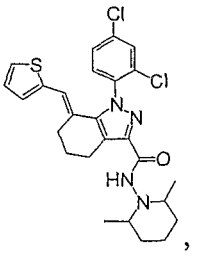
341 MS 514.1 MH^+



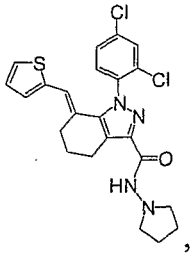
342 MS 487 MH^+



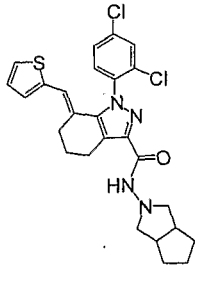
343 MS 501.1 MH^+



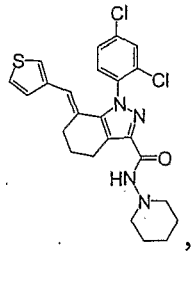
344 MS 515.1 MH^+



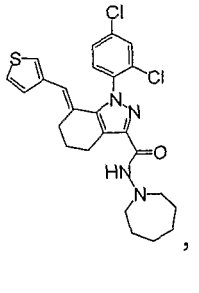
345 MS 473.1 MH^+



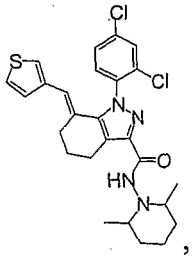
346 MS 513 MH^+



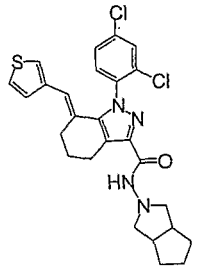
347 MS 487.1 MH^+



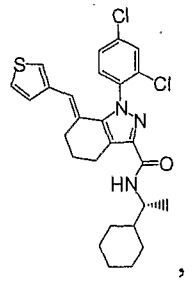
348 MS 501.1 MH^+



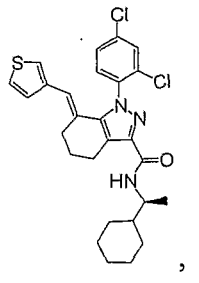
349 MS 515.1 MH^+



350 MS 513.2 MH^+

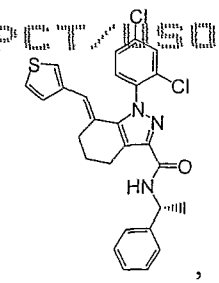


351 MS 514.2 MH^+

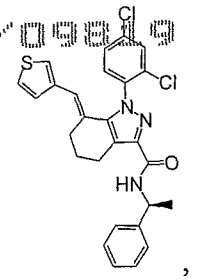


352 MS 514 MH^+

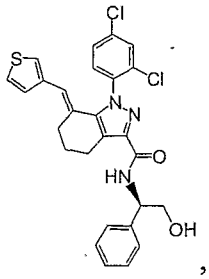
PCT/US05/09819



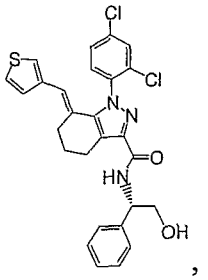
353 MS 507.9 MH^+



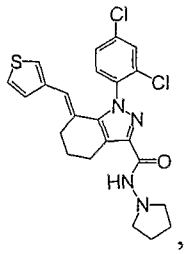
354 MS 507.9 MH^+



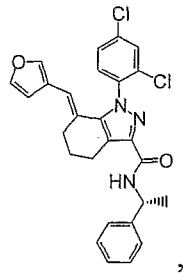
355 MS 524.1 MH^+



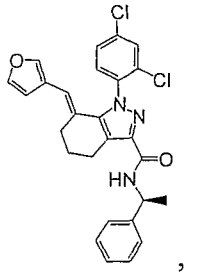
356 MS 524.1 MH^+



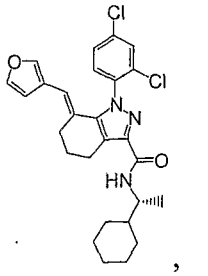
357 MS 473.1 MH^+



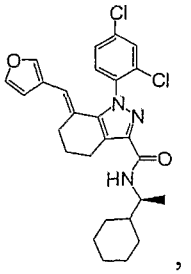
358 MS 492.1 MH^+



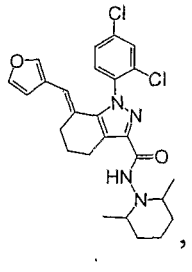
359 MS 492.1 MH^+



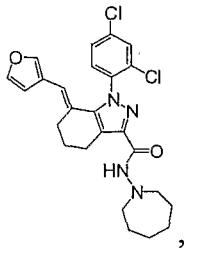
360 MS 498 MH^+



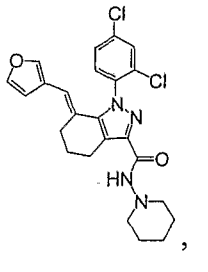
361 MS 498.1 MH^+



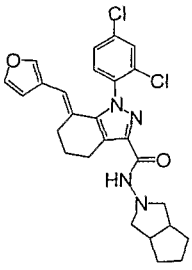
362 MS 499 MH^+



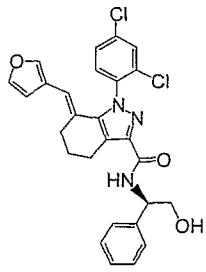
363 MS 485.1 MH^+



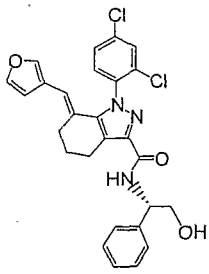
364 MS 472.1 MH^+



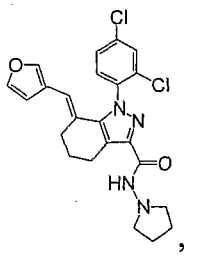
365 MS 497.1 MH^+



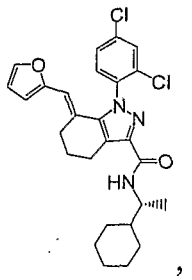
366 MS 510 MH^+



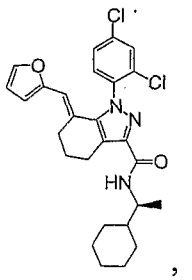
367 MS 509 MH^+



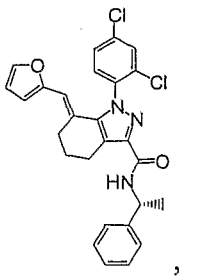
368 MS 457 MH^+



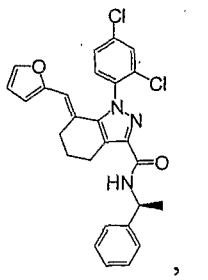
369 MS 498 MH^+



370 MS 498.1 MH^+

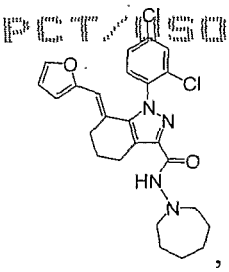


371 MS 492.1 MH^+

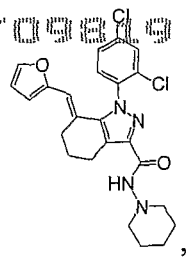


372 MS 492 MH^+

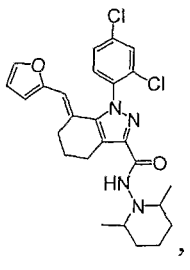
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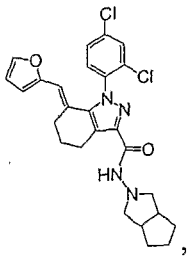
373 MS 485 MH^+



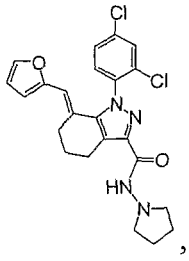
374 MS 471 MH^+



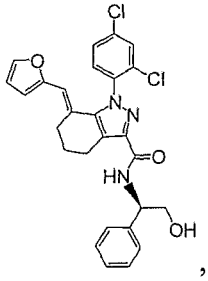
375 MS 499 MH^+



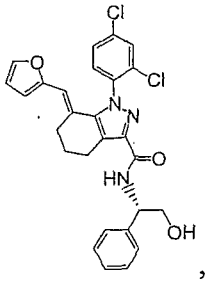
376 MS 498 MH^+



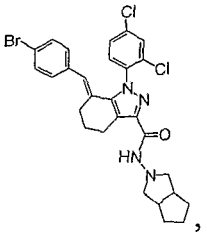
377 MS 457.1 MH^+



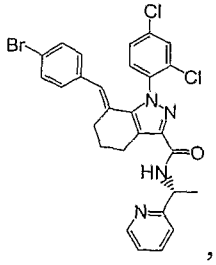
378 MS 507.9 MH^+



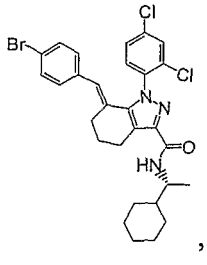
379 MS 508 MH^+



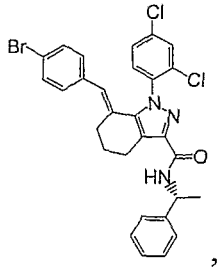
380 MS 585 MH^+



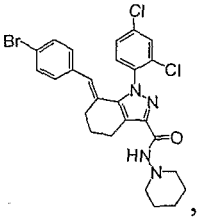
381 MS 581 MH^+



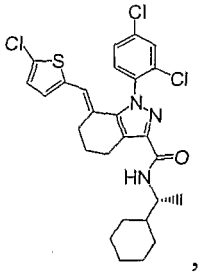
382 MS 586 MH^+



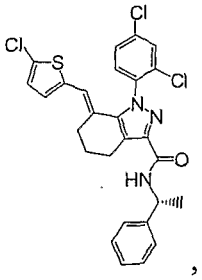
383 MS 580 MH^+



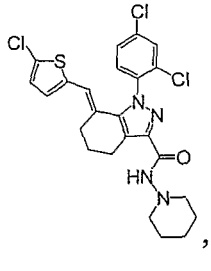
384 MS 559 MH^+



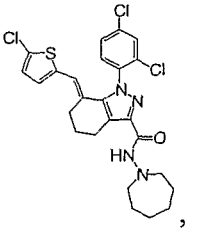
385 MS 549 MH^+



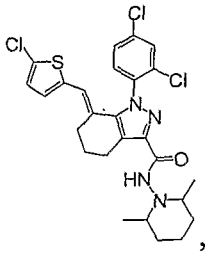
386 MS 544 MH^+



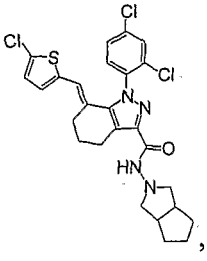
387 MS 522 MH^+



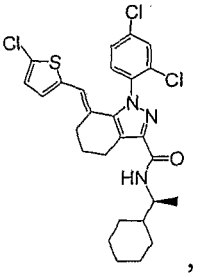
388 MS 537.1 MH^+



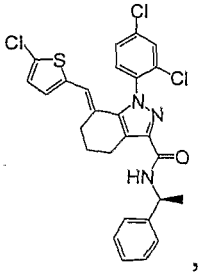
389 MS 548.1 MH^+



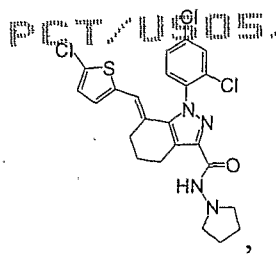
390 MS 547 MH^+



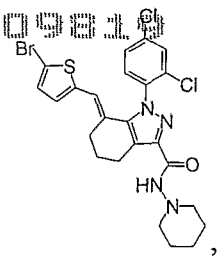
391 MS 548 MH^+



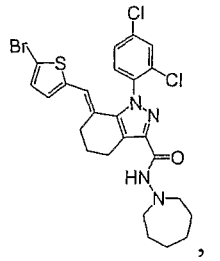
392 MS 542 MH^+



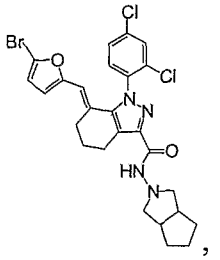
393 MS 506.9 MH^+



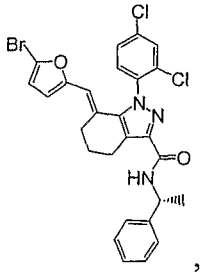
394 MS 550.9 MH^+



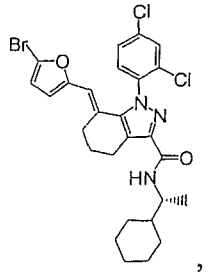
395 MS 564.9 MH^+



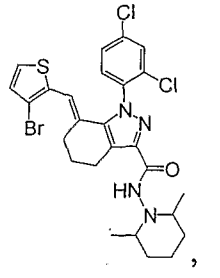
396 MS 577.1 MH^+



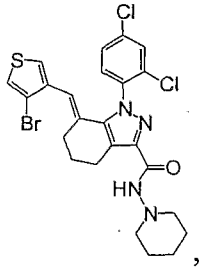
397 MS 571.8 MH^+



398 MS 578 MH^+



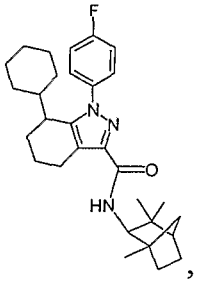
399 MS 595.0 MH^+



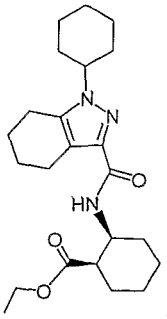
400 MS 567.0 MH^+

and pharmaceutically acceptable forms thereof.

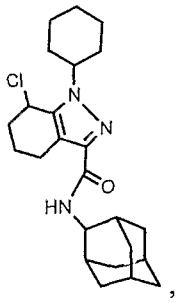
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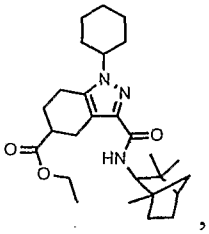
24 MS 478 MH^+



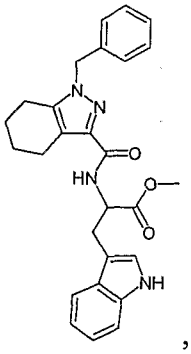
36 MS 402.1 MH^+



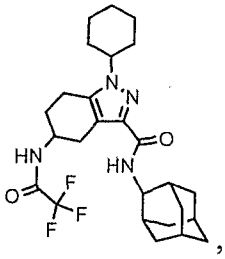
62 MS 416 MH^+



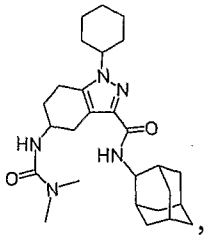
67 MS 456 MH^+



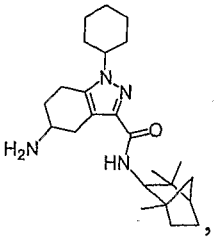
83 MS 457 MH^+



87 MS 493 MH^+

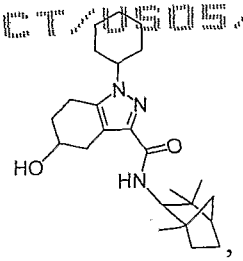


89 Example 9

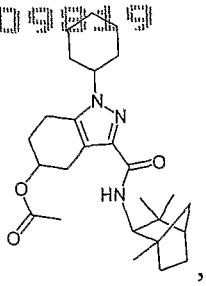


92 Example 8

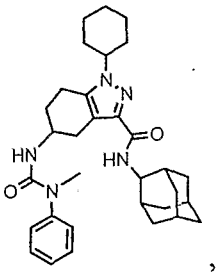
PCT/US05/09819



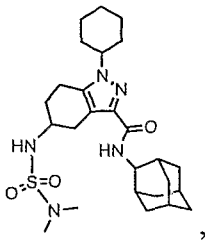
93 Example 8



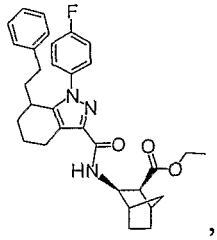
94 MS 442 MH^+



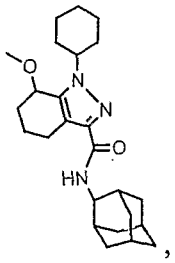
103 MS 530 MH^+



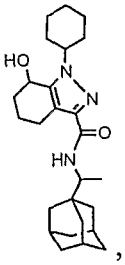
106 MS 504 MH^+



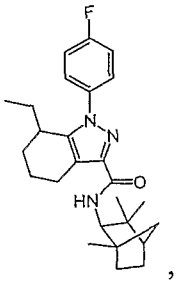
154 MS 530.2 MH^+



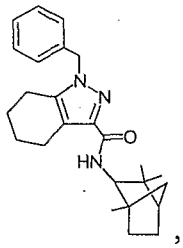
162 MS 412 MH^+



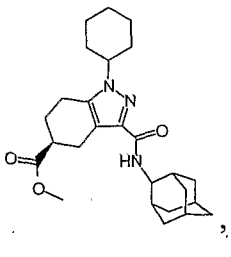
163 MS 425.8 MH^+



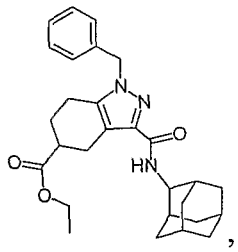
192 MS 424 MH^+



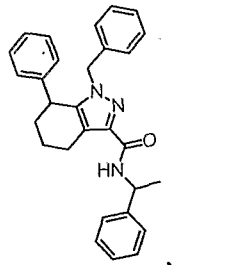
194 Example 2



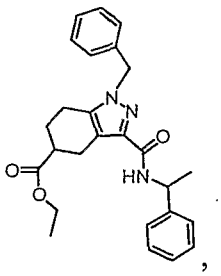
218 MS 440 MH^+



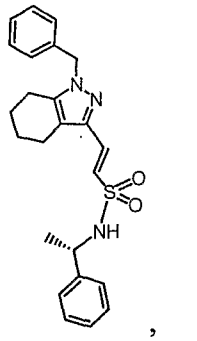
226 MS 462 MH^+



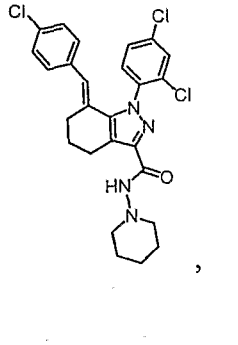
253 MS 436 MH^+



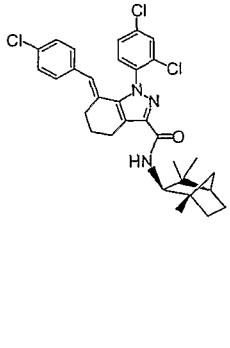
256 MS 432 MH^+



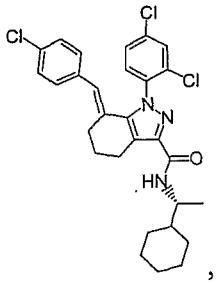
261 MS 422.1 MH^+



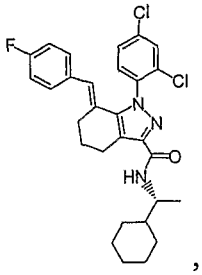
290 MS 515 MH^+



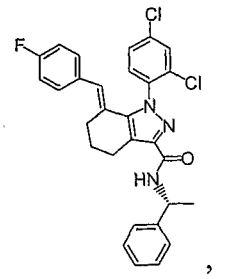
292 MS 568 MH^+



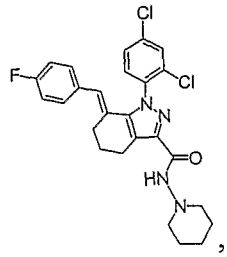
293 MS 542 MH^+



295 MS 526 MH^+

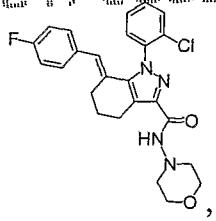


296 MS 520 MH^+

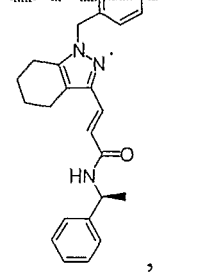


297 Example 10

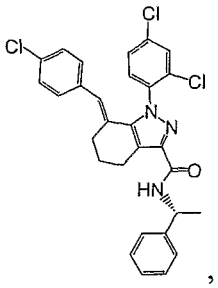
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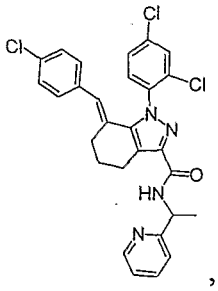
298 MS 501 MH^+



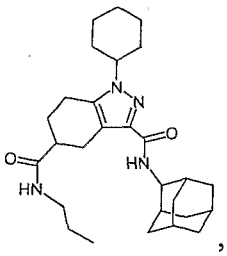
305 MS 386 MH^+



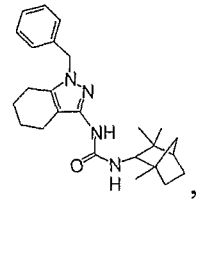
307 MS 536 MH^+



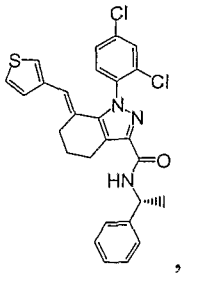
320 MS 537 MH^+



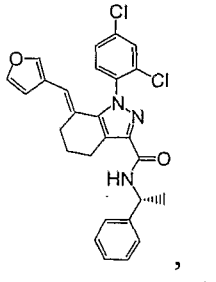
327 MS 467 MH^+



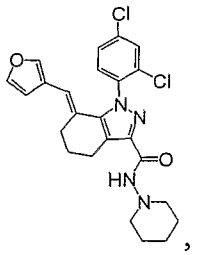
338 MS 407 MH^+



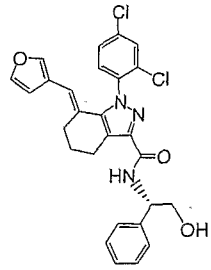
353 MS 507.9 MH^+



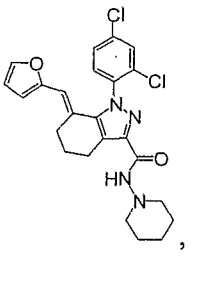
358 MS 492.1 MH^+



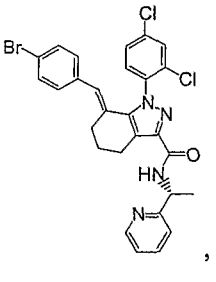
364 MS 472.1 MH^+



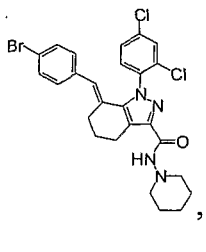
367 MS 509 MH^+



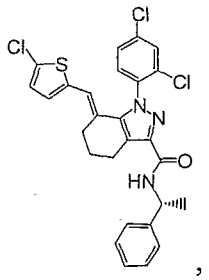
374 MS 471 MH^+



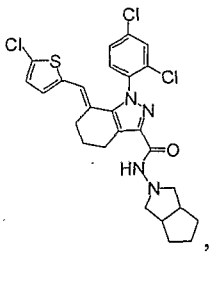
381 MS 581 MH^+



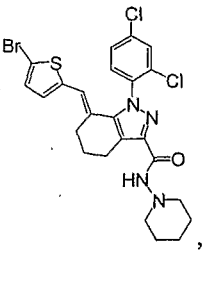
384 MS 559 MH^+



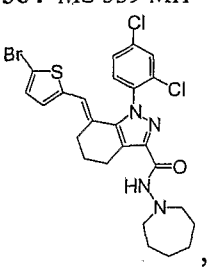
386 MS 544 MH^+



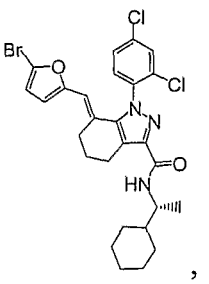
390 MS 547 MH^+



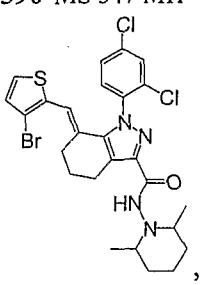
394 MS 550.9 MH^+



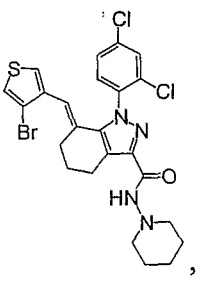
395 MS 564.9 MH^+



398 MS 578 MH^+



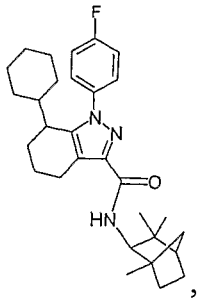
399 MS 595.0 MH^+



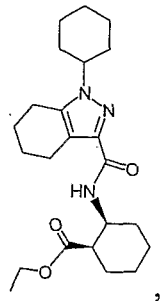
400 MS 567.0 MH^+

and pharmaceutically acceptable forms thereof.

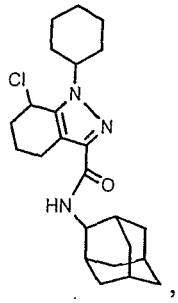
Another example of the present invention is a compound selected from:



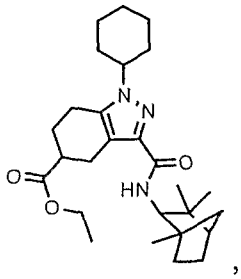
24 MS 478 MH^+



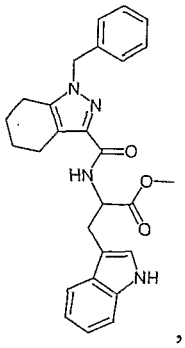
36 MS 402.1 MH^+



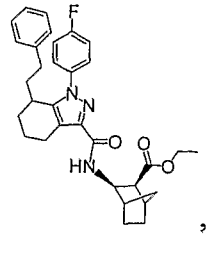
62 MS 416 MH^+



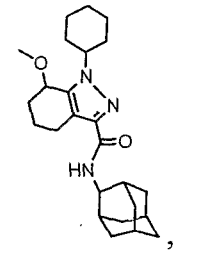
67 MS 456 MH^+



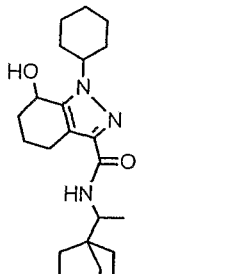
83 MS 457 MH^+



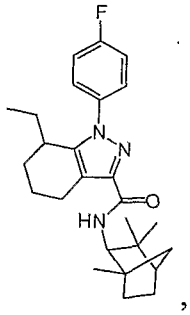
154 MS 530.2 MH^+



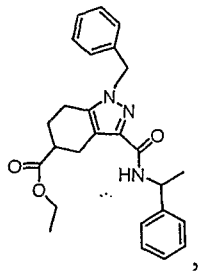
162 MS 412 MH^+



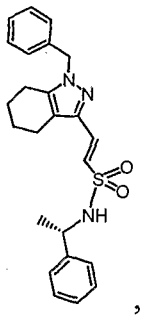
163 MS 425.8 MH^+



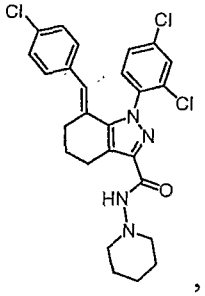
192 MS 424 MH^+



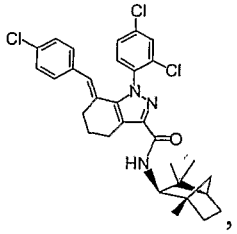
194 Example 2



226 MS 462 MH^+



253 MS 436 MH^+



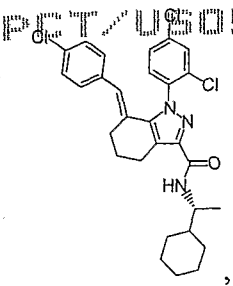
256 MS 432 MH^+

261 MS 422.1 MH^+

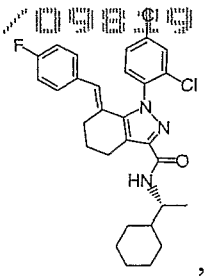
290 MS 515 MH^+

292 MS 568 MH^+

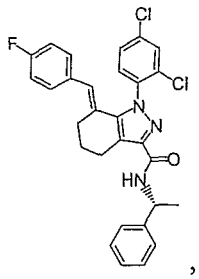
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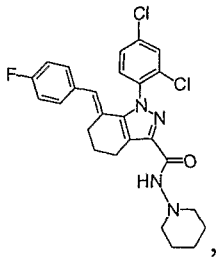
293 MS 542 MH^+



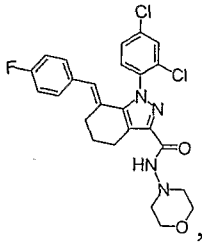
295 MS 526 MH^+



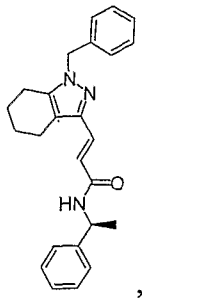
296 MS 520 MH^+



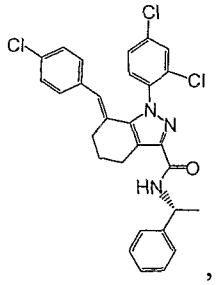
297 Example 10



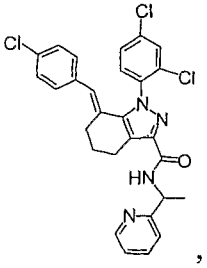
298 MS 501 MH^+



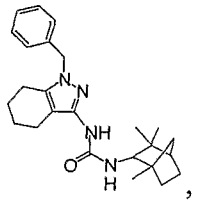
305 MS 386 MH^+



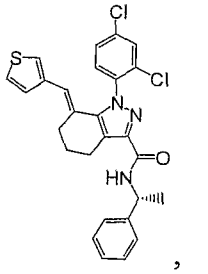
307 MS 536 MH^+



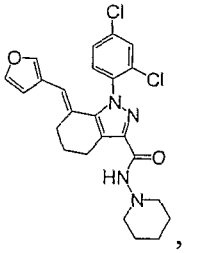
320 MS 537 MH^+



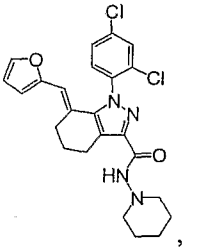
338 MS 407 MH^+



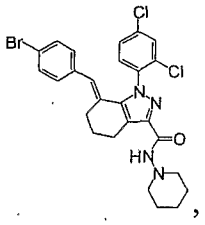
353 MS 507.9 MH^+



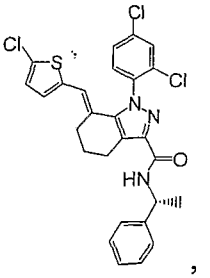
364 MS 472.1 MH^+



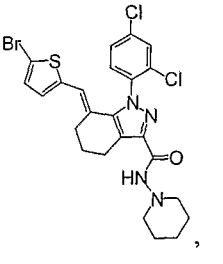
374 MS 471 MH^+



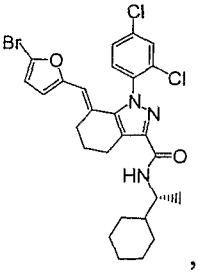
384 MS 559 MH^+



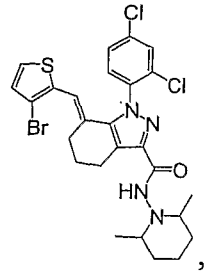
386 MS 544 MH^+



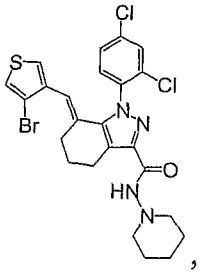
394 MS 550.9 MH^+



398 MS 578 MH^+



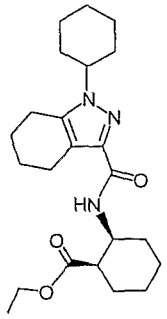
399 MS 595.0 MH^+



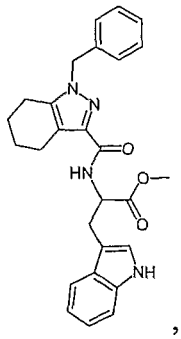
400 MS 567.0 MH^+

and pharmaceutically acceptable forms thereof.

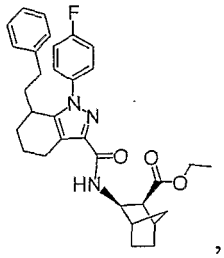
PCT / Another example of the present invention is a compound selected from:



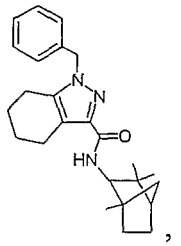
36 MS 402.1 MH^+



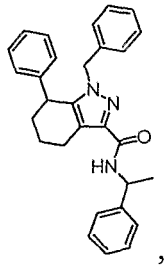
83 MS 457 MH^+



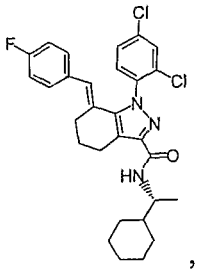
154 MS 530.2 MH^+



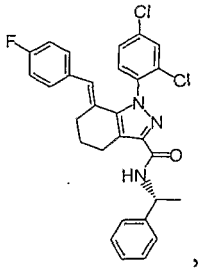
194 Example 2



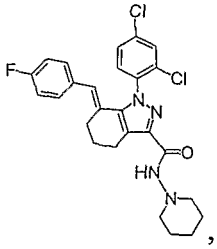
253 MS 436 MH^+



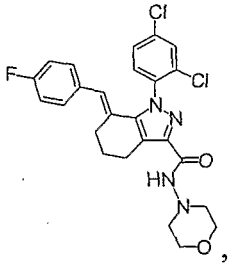
295 MS 526 MH^+



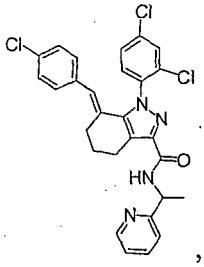
296 MS 520 MH^+



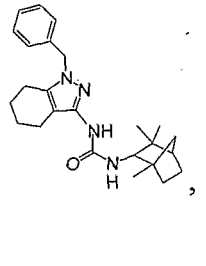
297 Example 10



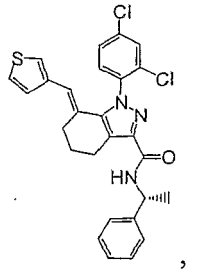
298 MS 501 MH^+



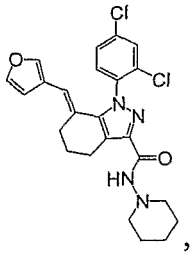
320 MS 537 MH^+



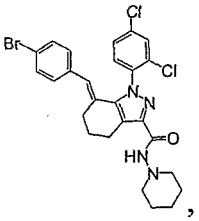
338 MS 407 MH^+



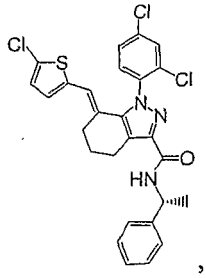
353 MS 507.9 MH^+



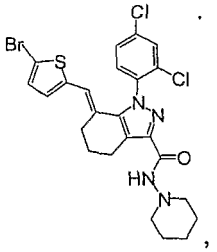
364 MS 472.1 MH^+



384 MS 559 MH^+

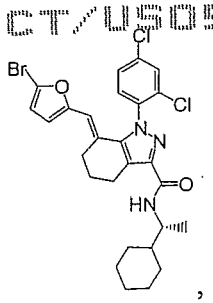


386 MS 544 MH^+

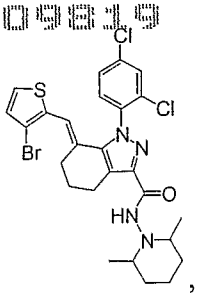


394 MS 550.9 MH^+

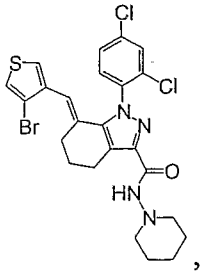
PCT/US05/09819



398 MS 578 MH^+



399 MS 595.0 MH^+



400 MS 567.0 MH^+

and pharmaceutically acceptable forms thereof.

DEFINITIONS

As used herein, the following terms have the following meanings:

The term "alkyl" means a saturated branched or straight chain monovalent hydrocarbon radical of up to 10 carbon atoms. Alkyl typically includes, but is not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, pentyl, hexyl, heptyl and the like.

The term "lower alkyl" means an alkyl radical of up to 4 carbon atoms. The point of attachment may be on any alkyl or lower alkyl carbon atom and, when further substituted, substituent variables may be placed on any carbon atom.

The term "alkylene" means a saturated branched or straight chain monovalent hydrocarbon linking group of up to 10 carbon atoms, whereby the linking group is derived by the removal of one hydrogen atom each from two carbon atoms. Alkylene typically includes, but is not limited to, methylene, ethylene, propylene, isopropylene, n-butylene, t-butylene, pentylene, hexylene, heptylene and the like. The term "lower alkylene" means an alkylene linking group of up to 4 carbon atoms. The point of attachment may be on any alkylene or lower alkylene carbon atom and, when further substituted, substituent variables may be placed on any carbon atom.

The term "alkylidene" means an alkylene linking group of from 1 to 10 carbon atoms having at least one double bond formed between two adjacent carbon atoms, wherein the double bond is derived by the removal of one hydrogen atom each from the two carbon atoms. Atoms may be oriented about the double bond in either the *cis* (E) or *trans* (Z) conformation. Alkylidene typically includes, but is not limited to, methylidene, vinylidene, propylidene, iso-propylidene, methallylene, allylidene (2-propenylidene), crotylene (2-butenylene), prenylene (3-methyl-2-butenylene) and the like. The term "lower alkylidene" means a radical or linking group of from 1 to 4

carbon atoms. The point of attachment may be on any alkylidene or lower alkylidene carbon atom and, when further substituted, substituent variables may be placed on any carbon atom.

The term "alkoxy" means an alkyl, alkylene or alkylidene radical of up to 10 carbon atoms attached via an oxygen atom, whereby the point of attachment is formed by the removal of the hydrogen atom from a hydroxide substituent on a parent radical. The term "lower alkoxy" means an alkyl, alkylene or alkylidene radical of up to 4 carbon atoms. Lower alkoxy typically includes, but is not limited to, methoxy, ethoxy, propoxy, butoxy and the like. When further substituted, substituent variables may be placed on any alkoxy carbon atom.

The term "cycloalkyl" means a saturated or partially unsaturated monocyclic, polycyclic or bridged hydrocarbon ring system radical or linking group. A ring of 3 to 20 carbon atoms may be designated by C_{3-20} cycloalkyl; a ring of 3 to 12 carbon atoms may be designated by C_{3-12} cycloalkyl, a ring of 3 to 8 carbon atoms may be designated by C_{3-8} cycloalkyl and the like.

Cycloalkyl typically includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, indanyl, indenyl, 1,2,3,4-tetrahydro-naphthalenyl, 5,6,7,8-tetrahydro-naphthalenyl, 6,7,8,9-tetrahydro-*5H*-benzocycloheptenyl, 5,6,7,8,9,10-hexahydro-benzocyclooctenyl, fluorenyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, bicyclo[2.2.2]octyl, bicyclo[3.1.1]heptyl, bicyclo[3.2.1]octyl, bicyclo[2.2.2]octenyl, bicyclo[3.2.1]octenyl, adamantanyl, octahydro-4,7-methano-1*H*-indenyl, octahydro-2,5-methano-pentalenyl and the like. When further substituted, substituent variables may be placed on any ring carbon atom.

The term "heterocyclyl" means a saturated, partially unsaturated or unsaturated monocyclic, polycyclic or bridged hydrocarbon ring system radical or linking group, wherein at least one ring carbon atom has been replaced with one or more heteroatoms independently selected from N, O or S. A heterocyclyl ring system further includes a ring system having up to 4 nitrogen atom ring members or a ring system having from 0 to 3 nitrogen atom ring members and 1 oxygen or sulfur atom ring member. When allowed by available valences, up to two adjacent ring members may be a heteroatom, wherein one heteroatom is nitrogen and the other is selected from N, O or S. A heterocyclyl radical is derived by the removal of one hydrogen atom from a single

carbon or nitrogen ring atom. A heterocyclyl linking group is derived by the removal of two hydrogen atoms each from either carbon or nitrogen ring atoms.

Heterocyclyl typically includes, but is not limited to, furyl, thienyl, 2*H*-pyrrole, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, pyrrolyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2-imidazolinyl (also referred to as 4,5-dihydro-1*H*-imidazolyl), imidazolidinyl, 2-pyrazolinyl, pyrazolidinyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, tetrazolyl, 2*H*-pyran, 4*H*-pyran, pyridinyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, azepanyl, indolizinyl, indolyl, isoindolyl, 3*H*-indolyl, indolinyl, benzo[*b*]furyl, benzo[*b*]thienyl, 1*H*-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4*H*-quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalzinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl, pteridinyl, quinuclidinyl, hexahydro-1,4-diazepinyl, 1,3-benzodioxolyl (also known as 1,3-methylenedioxyphenyl), 2,3-dihydro-1,4-benzodioxinyl (also known as 1,4-ethylenedioxyphenyl), benzo-dihydro-furyl, benzo-tetrahydro-pyranyl, benzo-dihydro-thienyl, 5,6,7,8-tetrahydro-4*H*-cyclohepta(*b*)thienyl, 5,6,7-trihydro-4*H*-cyclohexa(*b*)thienyl, 5,6-dihydro-4*H*-cyclopenta(*b*)thienyl, 2-aza-bicyclo[2.2.1]heptyl, 1-aza-bicyclo[2.2.2]octyl, 8-aza-bicyclo[3.2.1]octyl, 7-oxa-bicyclo[2.2.1]heptyl and the like.

The term "aryl" means an unsaturated, conjugated π electron monocyclic or polycyclic hydrocarbon ring system radical or linking group of 6, 9, 10 or 14 carbon atoms. An aryl radical is derived by the removal of one hydrogen atom from a single carbon ring atom. An arylene linking group is derived by the removal of two hydrogen atoms each of two carbon ring atoms. Aryl typically includes, but is not limited to, phenyl, naphthalenyl, azulenyl, anthracenyl and the like.

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

The term "alkoxycarbonyl" means a radical of the formula -C(O)O-alkyl.

The term "carboxy" means a radical of the formula -COOH or $-CO_2H$.

The term "aryloxy" means a radical of the formula -O-aryl.

The term "aryloxycarbonyl" means a radical of the formula -C(O)O-aryl.

The term "arylalkoxycarbonyl" means a radical of the formula -C(O)O-alkyl-aryl.

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

PCT The term "substituted" means one or more hydrogen atoms on a core molecule have been replaced with one or more radicals or linking groups, wherein the linking group, by definition is also further substituted.

The term "dependently selected" means one or more substituent variables are present in a specified combination (e.g. groups of substituents commonly appearing in a tabular list).

The substituent nomenclature used in the disclosure of the present invention was derived using nomenclature rules well known to those skilled in the art (e.g., IUPAC).

PHARMACEUTICAL PREPARATIONS AND METHODS OF USE

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicines, the salts of the compounds of this invention refer to non-toxic "pharmaceutically acceptable salts." FDA approved pharmaceutically acceptable salt forms (*Ref. International J. Pharm.* 1986, 33, 201-217; *J. Pharm. Sci.*, **1977**, Jan, 66(1), p1) include pharmaceutically acceptable acidic/anionic or basic/cationic salts.

Pharmaceutically acceptable acidic/anionic salts include, and are not limited to acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate and triethiodide. Organic or inorganic acids also include, and are not limited to, hydroiodic, perchloric, sulfuric, phosphoric, propionic, glycolic, methanesulfonic, hydroxyethanesulfonic, oxalic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, saccharinic or trifluoroacetic acid.

Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, 2-amino-2-hydroxymethyl-propane-1,3-diol (also known as tris(hydroxymethyl)aminomethane, tromethane or "TRIS"), ammonia, benzathine, *t*-butylamine, calcium, calcium gluconate, calcium hydroxide, chloroprocaine, choline,

choline bicarbonate, choline chloride, cyclohexylamine, diethanolamine, ethylenediamine, lithium, LiOMe, L-lysine, magnesium, meglumine, NH_3, NH_4OH, N-methyl-D-glucamine, piperidine, potassium, potassium-*t*-butoxide, potassium hydroxide (aqueous), procaine, quinine, sodium, sodium carbonate, sodium-2-ethylhexanoate (SEH), sodium hydroxide, triethanolamine (TEA) or zinc.

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

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

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

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

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

of polarized light (stereoisomers).

The term "stereoisomer" refers to isomers of identical constitution that differ in the arrangement of their atoms in space. Enantiomers and diastereomers are stereoisomers wherein an asymmetrically substituted carbon atom acts as a chiral center. The term "chiral" refers to a molecule that is not superposable on its mirror image, implying the absence of an axis and a plane or center of symmetry. The term "enantiomer" refers to one of a pair of molecular species that are mirror images of each other and are not superposable. The term "diastereomer" refers to stereoisomers that are not related as mirror images. The symbols "*R*" and "*S*" represent the configuration of substituents around a chiral carbon atom(s). The symbols "*R**" and "*S**" denote the relative configurations of substituents around a chiral carbon atom(s). .

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

The term "geometric isomer" refers to isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring or to a bridged bicyclic system. Substituent atoms (other than H) on each side of a carbon-carbon double bond may be in an E or Z configuration. In the "E" (opposite sided) or "chair" configuration, the substituents are on opposite sides in relationship to the carbon- carbon double bond; in the "Z" (same sided) or "boat" configuration, the substituents are oriented on the same side in relationship to the carbon-carbon double bond. Substituent atoms (other than H) attached to a carbocyclic ring may be in a cis or trans configuration. In the "cis" configuration, the substituents are on the same side in relationship to the plane of the ring; in the "trans" configuration, the substituents are on opposite sides in relationship to the plane of the ring. Compounds having a mixture of "cis" and "trans" species are designated "cis/trans". Substituent atoms (other than H) attached to a bridged bicyclic system may be in an "endo" or "exo" configuration. In the "endo" configuration, the substituents attached to a bridge (not a bridgehead) point toward the larger of the two remaining bridges; in the "exo" configuration, the substituents attached to a bridge point toward the smaller of the two remaining bridges.

It is to be understood that the various substituent stereoisomers, geometric isomers and mixtures thereof used to prepare compounds of the present invention are

either commercially available, can be prepared synthetically from commercially available starting materials or can be prepared as isomeric mixtures and then obtained as resolved isomers using techniques well-known to those of ordinary skill in the art.

The isomeric descriptors "R," "S," "S*," "R*," "E," "Z," "cis," "trans," "exo" and "endo" are used as described herein for indicating atom configuration(s) relative to a core molecule and are intended to be used as defined in the literature (IUPAC Recommendations for Fundamental Stereochemistry (Section E), *Pure Appl. Chem.*, **1976**, 45:13-30).

The compounds of the present invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the free base of each isomer of an isomeric pair using an optically active salt (followed by fractional crystallization and regeneration of the free base), forming an ester or amide of each of the isomers of an isomeric pair (followed by chromatographic separation and removal of the chiral auxiliary) or resolving an isomeric mixture of either a starting material or a final product using preparative TLC (thin layer chromatography) or a chiral HPLC column.

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

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

Therapeutic Use

CB1 and CB2 cannabinoid receptors belong to the G-protein-coupled receptor (GCPR) family, a receptor super-family with a distinctive pattern of seven transmembrane domains, which inhibits N-type calcium channels and /or adenylate cyclase to inhibit Q-type calcium channels. CB1 receptors are present in the CNS,

predominately expressed in brain regions associated with memory and movement such as the hippocampus (memory storage), cerebellum (coordination of motor function, posture and balance), basal ganglia (movement control), hypothalamus (thermal regulation, neuroendocrine release, appetite), spinal cord (nociception), cerebral cortex (emesis) and periphery regions such as lymphoid organs (cell mediated and innate immunity), vascular smooth muscle cells (blood pressure), gastrointestinal tract (duodenum, ileum and myenteric plexus for emesis control), lung smooth muscle cells (bronchodilation), eye ciliary body (intraocular pressure). CB2 receptors appear to be primarily expressed peripherally in lymphoid tissue (cell mediated and innate immunity), peripheral nerve terminals (peripheral nervous system), spleen immune cells (immune system modulation) and retina (intraocular pressure) and in the CNS in cerebellar granule cell mRNA (coordination of motor function). Pharmacological and physiological evidence also suggests that there may be other cannabinoid receptor subtypes that have yet to be cloned and characterized.

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

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

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

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

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

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

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

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

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the subject and/or assists the subject in losing weight.

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

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

A compound of formulae (I), (Ia), (Ib) or (Ic) for use as a CB receptor modulator includes a compound having a mean inhibition constant (IC_{50}) for CB receptor binding activity of between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 1 nM.

A compound of formulae (I), (Ia), (Ib) or (Ic) for use as a CB receptor modulator of the invention includes a compound having a CB1 agonist IC_{50} for CB1 agonist binding activity of between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 1 nM.

A compound of formulae (I), (Ia), (Ib) or (Ic) for use as a CB receptor modulator of the invention includes a compound having a CB1 antagonist IC_{50} for CB1 antagonist binding activity of between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200

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nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 1 nM.

A compound of formulae (I), (Ia), (Ib) or (Ic) for use as a CB receptor modulator of the invention includes a compound having a CB1 inverse-agonist IC_{50} for CB1 inverse-agonist binding activity of between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 1 nM.

A compound of formulae (I), (Ia), (Ib) or (Ic) for use as a CB receptor modulator of the invention includes a compound having a CB2 agonist IC_{50} for CB2 agonist binding activity of between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 1 nM.

A compound of formulae (I), (Ia), (Ib) or (Ic) for use as a CB receptor modulator of the invention includes a compound having a CB2 antagonist IC_{50} for CB2 antagonist binding activity of between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 1 nM.

A compound of formulae (I), (Ia), (Ib) or (Ic) for use as a CB receptor modulator of the invention includes a compound having a CB2 inverse-agonist IC_{50} for CB2 inverse-agonist binding activity of between about 5 μM to about 0.01 nM; between about 1 μM to about 0.01 nM; between about 800 nM to about 0.01 nM; between about 200 nM to about 0.01 nM; between about 100 nM to about 0.01 nM; between about 80 nM to about 0.01 nM; between about 20 nM to about 0.01 nM; between about 10 nM to about 0.1 nM; or about 1 nM.

The term "cannabinoid receptor" refers to any one of the known or heretofore

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

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

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

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

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

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

The term "administering" is to be interpreted in accordance with the methods of the present invention. Such methods include therapeutically or prophylactically

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administering an effective amount of a composition or medicament of the present invention at different times during the course of a therapy or concurrently as a product in a combination form.

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

The term "effective amount" refers to that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the syndrome, disorder or disease being treated. The effective amount of a compound of the invention is from about 0.001 mg/kg/day to about 300 mg/kg/day.

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

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

For example, the effective amount of a combination product and/or therapy comprising administration of a compound of formula (I) and topiramate would be the amount of the compound of formula (I) and the amount of topiramate that when taken together or sequentially have a combined effect that is effective. Further, it will be recognized by one skilled in the art that in the case of combination product and/or therapy with an effective amount, as in the example above, the amount of the compound of formula (I) and/or the amount of the anticonvulsant (e.g., topiramate) individually may or may not be effective.

Wherein the present invention is directed to the administration of a combination product and/or therapy, the instant compound and the anticonvulsant or contraceptive

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

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

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

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

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

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

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

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movement, immune, inflammation, cell growth, pain or neurodegenerative related syndromes, disorders or diseases.

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

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

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

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

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

Type II diabetes mellitus is characterized by the following clinical signs or symptoms: persistently elevated plasma glucose concentration or hyperglycemia; polyuria; polydipsia and / or polyphagia; chronic microvascular complications such as retinopathy, nephropathy and neuropathy; and macrovascular complications such as hyperlipidemia and hypertension. These micro-and macro-vascular complications can lead to blindness, end-stage renal disease, limb amputation and myocardial infarction.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

the present invention or composition thereof.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Such pharmaceutical compositions are particularly useful for treating a subject suffering from a metabolism related syndrome, disorder or disease, an appetite related syndrome, disorder or disease, a diabetes related syndrome, disorder or disease, an obesity related syndrome, disorder or disease, or a learning, cognition or memory related syndrome, disorder or disease.

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

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

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

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

For use in the methods of the present invention in combination with a compound of the formula (I), (Ia), (Ib) or (Ic), carbamazepine can be administered in the range of about 200 to about 1200 mg/day; preferably, about 400 mg/day.

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

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

compound of the formula (I), (Ia), (Ib) or (Ic), valproic acid can be administered in the range of about 250 to about 2500 mg/day; preferably, about 1000 mg/day.

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

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

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

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

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

For use in the methods of the present invention in combination with a compound of the formula (I), (Ia), (Ib) or (Ic), phenytoin sodium can be administered in the range of about 100 to about 500 mg/day; preferably, about 300 to about 400 mg/day; most preferably, about 300 mg/day.

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

Contraceptives suitable for use in a combination product and/or therapy include, for example, ORTHO CYCLEN®, ORTHO TRI-CYCLEN®, ORTHO TRI-CYCLEN

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

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

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

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

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

Pharmaceutical compositions of the invention may, alternatively or in addition to a compound of formula (I), (Ia), (Ib) or (Ic), comprise a pharmaceutically acceptable salt of a compound of formula (I), (Ia), (Ib) or (Ic) or a prodrug or pharmaceutically active metabolite of such a compound or salt in admixture with a pharmaceutically acceptable carrier.

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

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

Since both clinical and veterinary uses are equally included within the scope of

the present invention, a pharmaceutically acceptable formulation would include a composition or medicament formulation for either clinical or veterinary use.

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

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

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

evenly throughout the mixture) which may be readily subdivided into dosage units containing equal amounts of a compound of the present invention.

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

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

The liquid forms in which a compound of the present invention may be incorporated for oral administration include (without limitation), aqueous solutions, suitably flavored syrups, aqueous or oil suspensions (using a suitable synthetic or natural gum dispersing or suspending agent such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone, gelatin and the like), flavored emulsions (using a suitable edible oil such as cottonseed oil, sesame oil, coconut oil, peanut oil and the like), elixirs and other similar liquid forms with a variety of pharmaceutically acceptable vehicles.

As is also known in the art, the compounds may alternatively be administered parenterally via injection. For parenteral administration, sterile solutions or injectable suspensions may be parenteral vehicles wherein appropriate liquid carriers, suspending agents and the like are employed. Sterile solutions are a preferred parenteral vehicle. Isotonic preparations that generally contain suitable preservatives are employed when intravenous administration is desired. A parenteral formulation may consist of the active

ingredient dissolved in or mixed with an appropriate inert liquid carrier. Acceptable liquid carriers comprise aqueous solvents and the like and other optional ingredients for aiding solubility or preservation. Such aqueous solvents include sterile water, Ringer's solution or an isotonic aqueous saline solution. Alternatively, a sterile non-volatile oil may be employed as a solvent agent. Other optional ingredients include vegetable oils (such as peanut oil, cottonseed oil, sesame oil and the like), organic solvents (such as solketal, glycerol, formyl and the like), preservatives, isotonizers, solubilizers, stabilizers, pain-soothing agents and the like. A parenteral formulation is prepared by dissolving or suspending the active ingredient in the liquid carrier whereby the final dosage unit contains from 0.005 to 10% by weight of the active ingredient.

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

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

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

Depending on the subject and disease to be treated, the prophylactically or

therapeutically effective amount for a person of average body weight of about 70 kg per day may range from about 0.01 μg/kg to about 300 mg/kg; from about 0.1 μg/kg to about 200 mg/kg; from about 0.5 μg/kg to about 100 mg/kg; or, from about 1 μg/kg to about 50 mg/kg.

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

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

SYNTHETIC METHODS

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

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

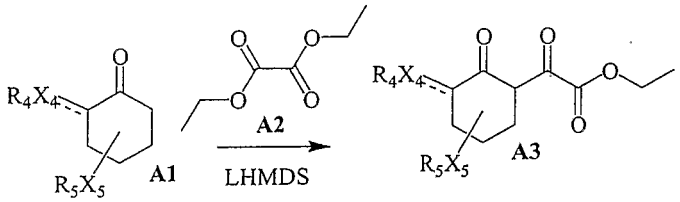
Boc	tert-butoxy carbonyl
Cpd	compound
DMF	N,N-dimethyl formamide

EtOAc	ethyl acetate
Et_2O	anhydrous ether
KOH	potassium hydroxide
LHMDS	lithium hexamethyl disilane
LiOH	lithium hydroxide
min/hr(s)/d(s)/mp	minute/hour(s)/day(s)/melting point
N_2	nitrogen
RT/rt/r.t.	room temperature
TEA or Et_3N	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Except where indicated, all reagents, solvents and starting materials are commercially available and were used without further purification. Where a particular component or piece of equipment was used, such are also commercially available.

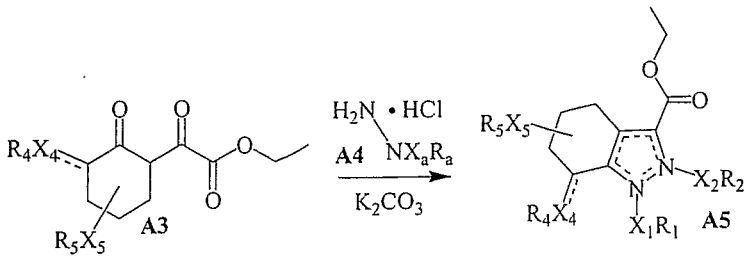
Scheme A

Synthesis of Tetrahydro-Indazole Compounds



An optionally substituted cyclohexanone Compound **A1** in solution (with one or more of Et_2O, THF and the like) is rapidly added to a reagent solution (containing a mixture of LHMDS and the like in one or more of Et_2O or THF and the like) at a temperature of about –78 °C under an inert atmosphere (using nitrogen and the like) and stirred at about -78 °C for about 40 mins. An optionally substituted oxalic acid di-ethyl ester Compound **A2** in solution (with Et_2O and the like) is then added to the Compound **A1** mixture.

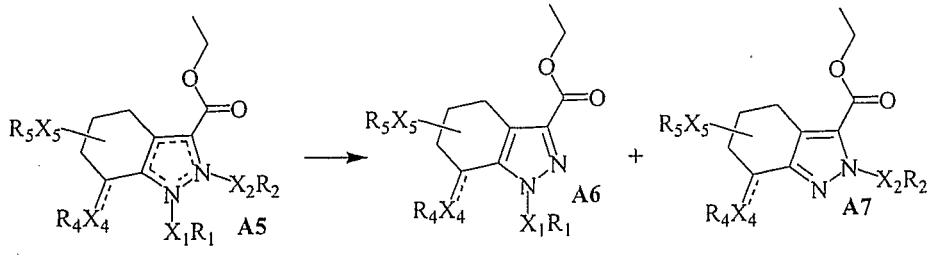
The reaction mixture is stirred at about –78 °C for about 1 hr, then allowed to warm to r.t. over an additional 2 hr period of time. The reaction is quenched (using saturated NH_4Cl, 1N HCl and the like) and the organic layer is extracted (with one or more of EtOAc, Et_2O and the like) and washed (with brine and the like), then separated and dried (with anhydrous sodium sulfate and the like). The extract is filtered and concentrated *in vacuo* to yield an optionally substituted oxo-(2-oxo-cyclohexyl)-acetic acid alkyl ester Compound **A3** as a crude product used without further purification in the next step.



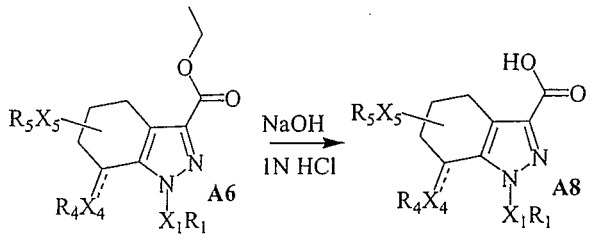
A substituted hydrazine hydrochloride Compound **A4** and K_2CO_3 (potassium carbonate) are added to Compound **A3** in solution (with one or more of MeOH, EtOH, CH_2Cl_2 and the like) at room temperature under an inert atmosphere. The reaction mixture is stirred overnight, then concentrated and diluted (with one or more of water, EtOAc (ethyl acetate) and the like). The organic layer is washed, separated and dried, then filtered and concentrated *in vacuo* to yield a crude product Compound **A5** as a mixture of isomers, wherein a mixture of X_1R_1 and X_2R_2 isomers are present. The X_aR_a substituent moiety on Compound **A4** represents the possibility that, after separation, the substituted amine group may be found either on the N^1 position as X_1R_1 or on the N^2 position as X_2R_2.

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

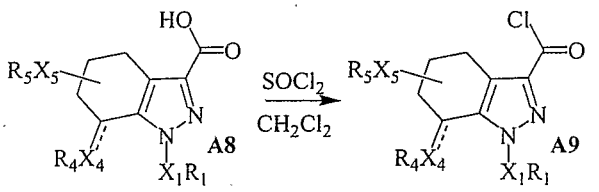
As illustrated in this Scheme, Compound **A4** may also be further substituted with a variety of X_aR_a substituents (as previously defined herein). In many instances, the substituted hydrazine Compound **A4** is commercially available. When not commercially available, a particularly substituted Compound **A4** may be prepared by methods known to those skilled in the art. More specifically, a halogenated X_aR_a substituent moiety is reacted with a hydrazine hydrate solution at reflux and used without further purification as Compound **A4** (as described more completely in Example 3).



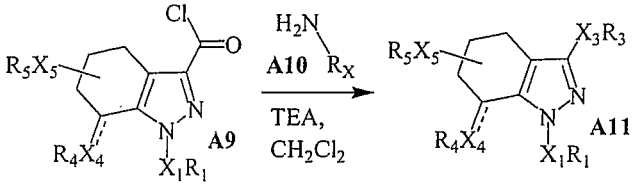
The Compound **A5** isomeric mixture is separated via flash chromatography (eluted with a suitable solvent mixture such as 20% or 30% EtOAc:hexane and the like) to provide a purified major isomer Compound **A6** and a minor isomer Compound **A7**. The major isomer Compound **A6** is substituted on the N^1 position with X_1R_1 (X_2R_2 is necessarily absent). The minor isomer Compound **A7** is substituted on the N^2 position with X_2R_2 (wherein X_1R_1 is absent).



The separated major isomer Compound **A6** is treated with a reagent solution (such as a mixture of NaOH in a solvent such as THF or water and the like) and stirred overnight. The reaction is quenched and extracted with a solvent (such as CH_2Cl_2, EtOAc and the like). The organic layer is dried, filtered and concentrated *in vacuo* to yield Compound **A8**.



A reagent (such as $SOCl_2$ (thionyl chloride) and the like) in a solvent (such as CH_2Cl_2 and the like) is added to Compound **A8** at ambient temperature under an inert nitrogen atmosphere. The reaction mixture is stirred at reflux temperature for about 15 min, then concentrated *in vacuo* to afford the corresponding acid chloride intermediate Compound **A9**.



Compound **A9** (optionally in solution with TEA (triethylamine) and the like) is added to a solution of a substituted amine Compound **A10** (in a solvent such as CH_2Cl_2 and the like) at ambient temperature under an inert nitrogen atmosphere.

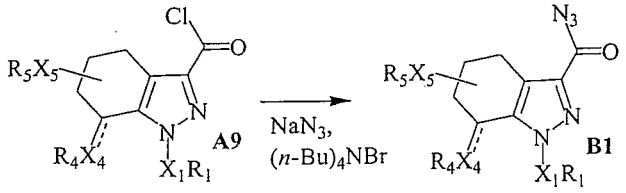
In general, Compound **A10** is a commercially available substituted amine.

When not commercially available, a particularly substituted amine Compound **A10** may be prepared by methods known to those skilled in the art.

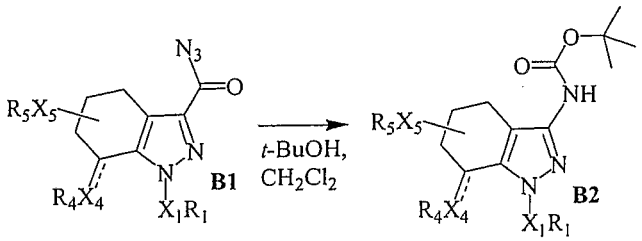
The Compound **A9/A10** mixture is stirred at about r.t. for a period of time, then diluted (with a mixture of water and CH_2Cl_2 and the like). The organic layer is separated and dried, then filtered and concentrated *in vacuo* to yield a crude product. The product is purified via flash chromatography (eluted with a solvent mixture such as 20% or 30% EtOAc in hexane) to provide a target Compound **A11**.

For purposes of illustration in this Scheme, the Compound **A11** X_3R_3 substituent moiety incorporates the C(O) portion of the C^3 substituent from Compound **A9** and the -NH- portion from Compound **A10**, wherein X_3 is absent and R_3 is either $-(R_6)C(O)Z_1R_7$ or $-(R_6)C(O)N(R_{9a})Z_2R_9$, and wherein R_6 is absent.

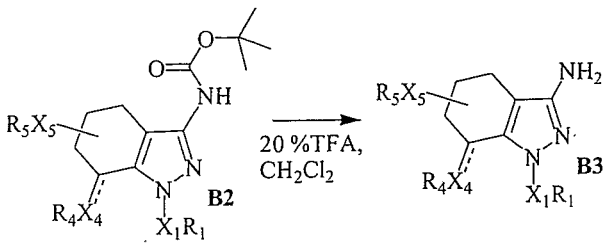
Scheme B



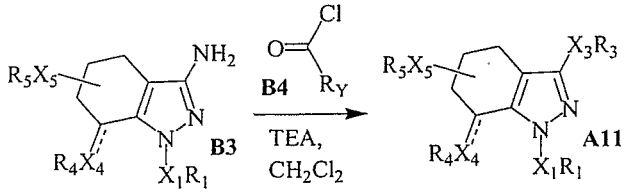
A catalytic amount of tetrabutylammonium bromide ($(n\text{-Bu})_4NBr$) is added to a solution of Compound **A9** (in a solvent such as DCE (dichloroethane) and the like) at 0°C. A saturated solution of NaN_3 (sodium azide) (in water) is added dropwise at 0°C. The reaction mixture is stirred for about 0.5 hrs, then diluted (with one or more of cold water, CH_2Cl_2 and the like). The organic layer is washed (with one or more of water, brine and the like) and dried (using sodium sulfate), then filtered and concentrated to give an azide Compound **B1**.



t-BuOH (*tert*-butanol) is added to a solution of Compound **B1** (in a solvent such as CH_2Cl_2 and the like) and the mixture is refluxed for about 48 hrs. The reaction product is concentrated and purified via silica gel column (eluted with a solvent mixture such as 10% EtOAc in hexane) to give a Boc-protected amine Compound **B2**.



TFA is added to a solution of Compound **B2** (in a solvent such as CH_2Cl_2 and the like) and the mixture is stirred overnight. The reaction product is concentrated and the residue is dissolved (in a solvent such as CH_2Cl_2 and the like) and washed (with one or more of 1N NaOH, water and the like) and dried (using sodium sulfate), then filtered and concentrated to give an amine Compound **B3**.



Compound **B3** (optionally in solution with TEA and the like) is added to a solution of a substituted amine Compound **B4** (in a solvent such as CH_2Cl_2 and the like) at ambient temperature under an inert nitrogen atmosphere. The mixture is stirred at r.t. for about 4 hrs, then concentrated and purified via silica gel column (eluted with a solvent mixture such as 15%, 20% or 30% EtOAc in hexane) to provide the target Compound **A11**.

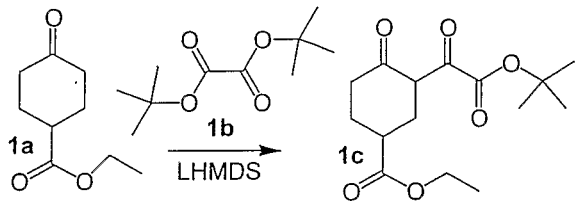
For purposes of illustration in this Scheme, the Compound **A11** X_3R_3 substituent moiety incorporates the NH portion of the C^3 substituent from Compound **B3** and the $R_YC(O)$- portion from Compound **B4**, wherein X_3 is a -NH- and R_3 is either $-(R_6)C(O)Z_1R_7$, $-SO_2N(R_8)R_{8a}$, or $-(R_6)C(O)N(R_{9a})Z_2R_9$, and wherein R_6 is absent.

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

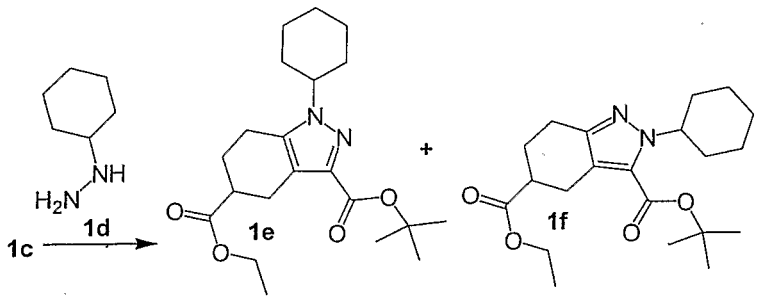
Example 1

(5*S*)-3-(adamantan-2-ylcarbamoyl)-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-5-carboxylic acid ethyl ester (Cpd **208**)

(5*R*)-3-(adamantan-2-ylcarbamoyl)-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-5-carboxylic acid ethyl ester (Cpd **209**)



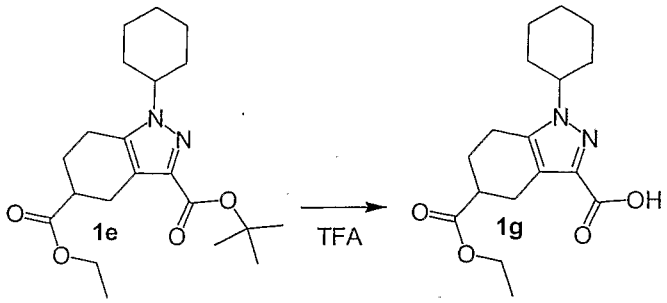
4-oxo-cyclohexanecarboxylic acid ethyl ester Compound **1a** (3.4 g, 0.02 mol) was added to LHMDS (20 mL, 1M in THF, 0.02 mol) in THF (15 mL) at about -78 °C under N_2 and stirred at –78 °C for 40 min. Then oxalic acid di-tert-butyl ester Compound **1b** (4.04 g, 0.02 mol) in THF (15 mL) was transferred into the mixture via cannula. The mixture was stirred for 1 hr at –78 °C and 2 hrs at r.t. The reaction was quenched with saturated NH_4Cl and the product was concentrated *in vacuo*, then extracted using EtOAc (30 mL). The EtOAc was evaporated to provide a crude 3-tert-butoxyoxalyl-4-oxo-cyclohexanecarboxylic acid ethyl ester Compound **1c** (5.0 g) which was used in the next step without further purification.



The crude Compound **1c** (2.98 g) was stirred with cyclohexyl hydrazine hydrochloride Compound **1d** (1.51 g, 0.01 mol) and K_2CO_3 (0.69 g, 0.005 mol) in CH_2Cl_2 (30 mL) under N_2 at r.t. overnight and then washed with water. The crude product was chromatographically purified (eluted with 30% EtOAc in hexane) to afford a mixture of a major isomer Compound **1e** (2.5 g, 66.5% yield from Compound **1a**) and a minor isomer Compound **1f** (0.3 g, 8.0% yield from Compound **1a**).

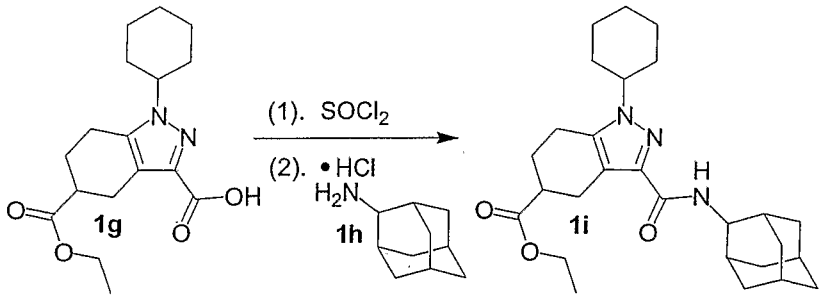
Compound **1e:** MS *m/z* 377 $(M+H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.18 (2H, q, J = 7.1 Hz), 3.95 (1H, m), 3.14 (1H, m), 2.82 (2H, m), 2.63 (2H, m), 2.21 (1H, m), 1.89 (6H, m), 1.66 (1H, m), 1.58 (9H, s), 1.29 (4H, m), 1.28 (3H, t, J = 7.1 Hz).

Compound **1f:** MS *m/z* 377 $(M+H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ: 5.02 (1H, m), 4.16 (2H, q, J = 7.2 Hz), 3.09 (1H, m), 2.82 (2H, m), 2.62 (2H, m), 2.21 (1H, m), 1.91 (6H, m), 1.69 (1H, m), 1.58 (9H, s), 1.25-1.45 (4H, m), 1.26 (3H, t, J = 7.2 Hz).

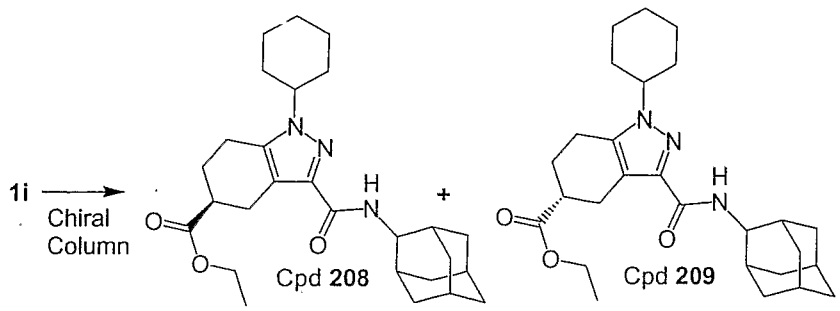


The separated major isomer Compound **1e** (4.2 g, 11.16 mMol) was treated with a 50% TFA/CH_2Cl_2 solution (20 mL) over about an 8 hr period (overnight). The solvent was evaporated and the residue was washed with CH_2Cl_2 to give 1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3,5-dicarboxylic acid 5-ethyl ester Compound **1g** (3.6 g, 100% yield) as a solid.

Compound **1g:** MS *m/z* 321 $(M+H)^+$, 343 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ: 4.23 (2H, q, J = 7.1 Hz), 4.13 (1H, m), 3.19 (1H, m), 2.85 (4H, m), 2.3 (1H, m), 1.92 (6H, m), 1.72 (1H, m), 1.32 (7H, m).



Compound **1g** (3.6 g, 11.2 mMol) was reacted with thionyl chloride (14 mL, 190 mMol) and refluxed for about 15 min to form an acid chloride intermediate. The intermediate was further reacted with a 2-adamantanamine hydrochloride Compound **1h** (2.09 gms, 11.16 mMol) in CH_2Cl_2. The crude product afforded was chromatographically purified (eluted with 30% EtOAc in hexane) to provide a 3-(adamantan-2-ylcarbamoyl)-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-5-carboxylic acid ethyl ester Compound **1i** (3.2 g, 63% yield) as a white solid racemate.

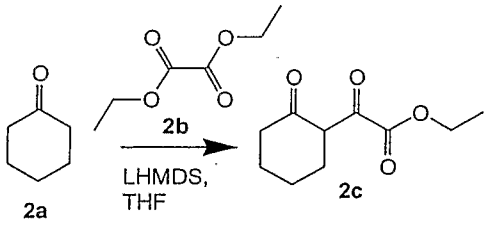


The racemic Compound **1i** was enantiomerically separated via chiral column chromatography (eluted with 90% hexane in IPA) to provide an (*S*)-enantiomer Compound **208** and an (*R*)-enantiomer Compound **209**.

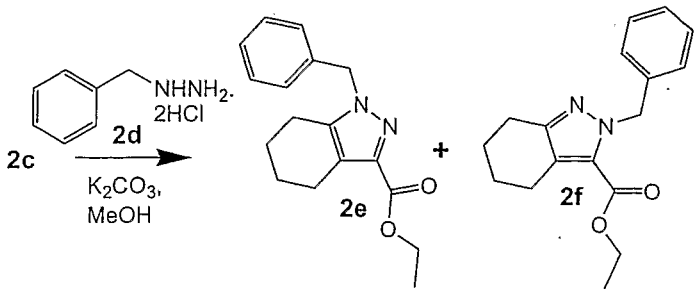
MS *m/z* 454 $(M+H)^+$, 476 $(M+Na)^+$; IR (KBr): 3419, 2908, 1732, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.25 (1H, d, J = 8.3 Hz), 4.22 (1H, m), 4.14 (2H, q, J = 7.1 Hz), 3.91 (1H, m), 3.32 (1H, dd, J = 16.4, 5.3 Hz), 2.83 (2H, m), 2.63 (2H, m), 2.20 (1H, m), 1.88 (23H, m), 1.32 (2H, m), 1.25 (3H, t, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.5, 162.8, 141.5, 138.3, 116.6, 60.8, 58.7, 52.9, 40.4, 38.0, 37.6, 33.0, 32.9, 32.54, 32.51, 32.47, 27.7, 27.6, 25.9, 25.5, 25.3, 24.9, 21.1, 14.6; Anal. Calcd for $C_{27}H_{39}N_3O_3$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.32; H, 8.77; N, 9.07.

Example 2

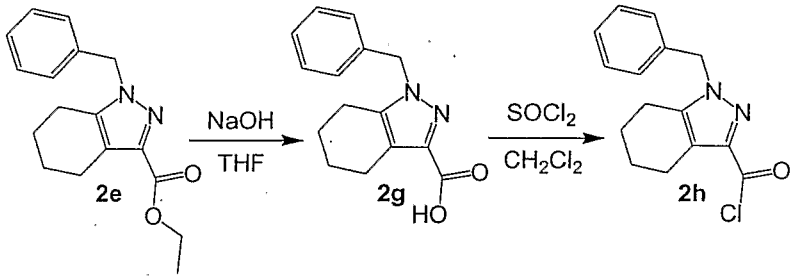
1-benzyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide (Cpd **194**)



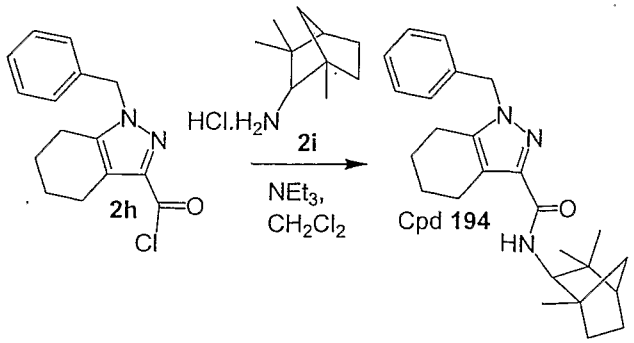
Cyclohexanone Compound **2a** (20.54 g, 0.25 mol) in Et_2O (100 mL) was added to a solution of LHMDS (250 mL, 0.25 mol) in Et_2O (400 mL) at –78 °C under a N_2 atmosphere. The mixture was maintained at –78 °C and stirred for 60 min. A diethyloxylate Compound **2b** (36.53 g, 0.25 mMol) in Et_2O (100 mL) was added to the mixture, which was stirred at –78 °C for 1 hr. The reaction mixture was allowed to warm to r.t. over 3 hrs and the reaction was quenched with 1N HCl (150 mL), The organic layer was extracted with Et_2O (200 mL), washed with brine and separated, then dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield 48.50 g, 95% of oxo-(2-oxo-cyclohexyl)-acetic acid ethyl ester Compound **2c** as a yellow oil. Compound **2c** was used in the next step without further purification.



Benzylhydrazine dihydrochloride Compound **2d** (1.75 g, 9.0 mMol) and K_2CO_3 (2.77 g, 19.5 mMol) were added to a solution of Compound **2c** (1.88 g, 8.85 mMol) in MeOH (50 mL) at ambient temperature under a N_2 atmosphere. The resultant heterogeneous mixture was stirred overnight. The reaction mixture was concentrated to dryness and diluted with H_2O (100 mL) and EtOAc (500 mL). The organic layer was washed with brine, separated, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield a product as a crude oil. Purification by flash chromatography (eluted with 20% EtOAc in hexane) afforded a major isomer 1-benzyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester Compound **2e** (1.51 g, 60%) and a minor isomer 2-benzyl-4,5,6,7-tetrahydro-2H-indazole-3-carboxylic acid ethyl ester Compound **2f** as a colorless oil.



1N NaOH (10 mL) was added to Compound **2e** (0.30 g, 1.05 mMol) in THF (10 mL). The mixture was stirred for 30 hours, acidified to pH 2 with 1N HCl and extracted with EtOAc (100 mL). The organic layer was washed with brine, dried over sodium sulfate, then filtered and concentrated *in vacuo* to yield 1-benzyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid Compound **2g** (0.190 g, 70%) as a white solid. Thionyl chloride (0.17 g, 0.39 mMol) was added to a solution of the carboxylic acid Compound **2g** (0.15 g, 0.55 mMol) in CH_2Cl_2 (10 mL) at ambient temperature under a N_2 atmosphere. The reaction was stirred for 3 hrs and concentrated *in vacuo* to afford the corresponding acid chloride Compound **2h** in quantitative yield.



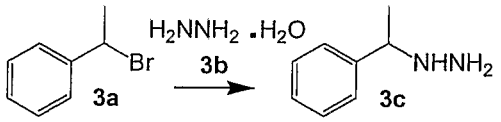
NEt_3 (triethylamine) (0.10 g, 0.98 mMol) and acid chloride Compound **2h** (0.17 g, 0.39 mMol) were added to a solution of 1,3,3-trimethyl-bicyclo[2.2.1]hept-2-ylamine hydrochloride Compound **2i** (0.071 g, , 0.39 mMol) (prepared from commercially available L(-)-fenchone as described in Suchocki JA; May EL; Martin TJ; Clifford G; Martin, BR, *J. Med Chem.*, **1991**, *34*, 1003) in CH_2Cl_2 (10 mL) at ambient temperature under a N_2 atmosphere.

The reaction was stirred at r.t. for 3 hrs, then diluted with water (10 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, dried with anhydrous sodium sulfate, filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (eluted with 20% EtOAc in hexane) afforded Compound **194** (0.09 g, 41%), as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.27 (m, 3H), 7.14-7.09 (m, 2H), 7.03-6.99 (d, *J*=12 Hz, 2H), 5.23 (s, 2H), 3.76-3.72(m, 1H), 2.85-2.80 (m, 1H), 2.44-2.40 (m, 1H), 1.80-1.70 (m, 7H), 1.55-1.42 (m, 2H), 1.24-1.28(m, 1H), 1.17 (s, 3H), 1.12 (s, 3H), 0.86 (s, 3H). MS *m/z* 392 (M^+).

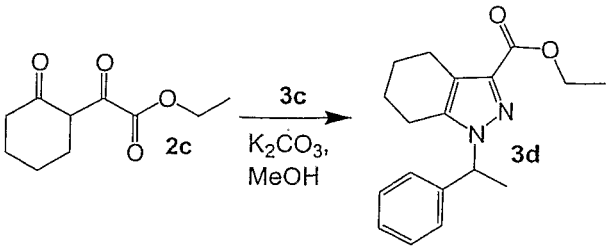
Example 3

1-(1-phenyl-ethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid [(1*S*)-1-cyclohexyl-ethyl]-amide (Cpd **249**)

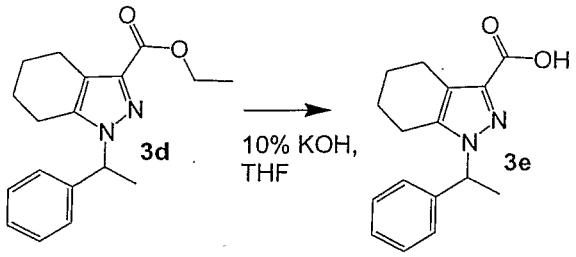


1-bromoethylbenzene Compound **3a** (8.0 mL, 58.0 mMol) was added to a solution of hydrazine hydrate Compound **3b** (20 mL) in THF (80 mL) which was then heated to reflux for 8 hrs. The solvent was removed *in vacuo* and Et_2O (100 mL) was added. The organic layer was washed with brine, separated and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield (1-phenyl-ethyl)-hydrazine Compound **3c** as a pale yellow oil (5.8 g), used in the next step without purification. MS *m/z* 137

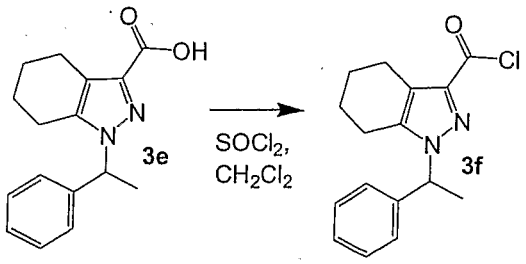
(M+H, 70%), 105 ($M-NHNH_2$, 100%).



Oxo-(2-oxo-cyclohexyl)-acetic acid ethyl ester Compound **2c** (3.97 g, 20.0 mMol) was added to a solution containing crude Compound **3c** (5.8 g, 29.0 mMol) and K_2CO_3 (0.2 g) in MeOH (40 mL). The suspension was stirred at r.t. for 48 hrs. The solvent was removed *in vacuo* and the residue was extracted with CH_2Cl_2. The organic layer was washed with water and brine, then separated and dried over Na_2SO_4 to provide Compound **3d** as a red oil (4.6 g), used in the next step without further purification. MS *m/z* 321 (M+Na, 100%).

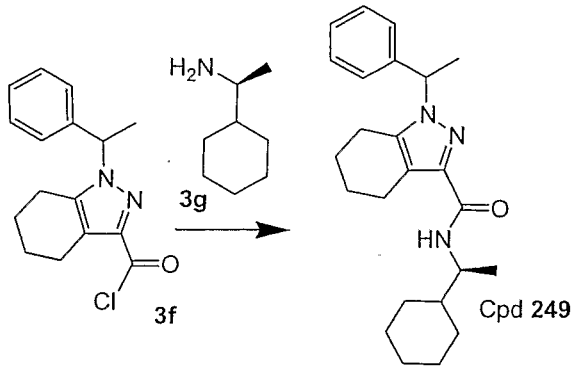


Compound **3d** was dissolved in a solution of KOH (5.6 g, 100 mMol) in THF (40 mL) and water (60 mL). The resulting solution was stirred at r.t. for 12 hrs, followed by removal of the THF *in vacuo*. The aqueous solution was extracted with Et_2O to remove impurities. The aqueous layer was then acidified with 6 N HCl and was extracted with Et_2O (2 x 50 mL). The organic layer was separated and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield 1-(1-phenyl-ethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid Compound **3e** as pale yellow solid. MS *m/z* (+ve mode) 293 (M+Na, 100%), MS *m/z* (-ve mode) 269 (M-H, 100%).



Compound **3e** (2.0 g, 7.4 mMol) was dissolved in CH_2Cl_2 (15 mL) and treated

with $SOCl_2$ (8.0 g). The resulting solution was heated to reflux for 3 hrs followed by removal of the solvent *in vacuo* to provide 1-(1-phenyl-ethyl)-4,5,6,7-tetrahydro-1H-indazole-3-carbonyl chloride Compound **3f** as a brownish yellow oil.

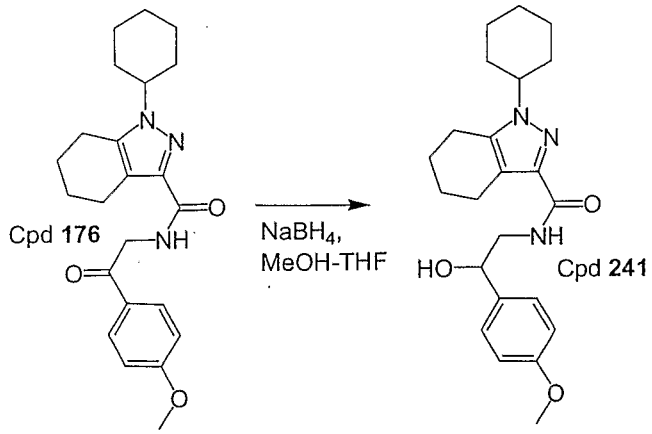


A solution of Compound **3f** (0.06 g, 0.2 mMol) in CH_2Cl_2 (1 mL) was added to a solution of commercially available (*S*)-1-cyclohexyl-ethylamine Compound **3g** (0.03 mL, 0.18 mMol) in CH_2Cl_2 (2 mL) and triethylamine (0.1 mL, 0.8 mMol) at 0 °C. The resulting suspension was stirred for 2 hrs, then the reaction was quenched with water (5 mL) and the mixture was extracted with Et_2O. The organic layer was washed with 10% NaOH and brine, then separated and dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by preparative TLC (1:1 hexane/EtOAc) to provide Compound **249** as a mixture of diastereomers in a brown oil. MS *m/z* 380 (M+H, 100%).

^{1}H NMR (300 MHZ, $CDCl_3$) δ 7.12-7.29 (m, 3H), 6.95-7.06 (m, 2H), 6.70 (br d, J = 6.0 Hz, 1H), 5.27 (q, J = 3.0 Hz, 1H), 3.84-4.01 (m, 1H), 2.72 (br t, 2 H), 2.30-2.45 (br m, 1H), 2.12-2.26 (br m, 1H), 1.82 (d, J = 6.0 Hz, 3H), 1.48-1.86 (br m, 8H), 1.27-1.42 (m, 1H), 1.12 (d, J = 6.0 Hz, 3H), 0.90-1.25 (br m, 6H).

Example 4

1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid [2-hydroxy-2-(4-methoxy-phenyl)-ethyl]-amide (Cpd **241**)

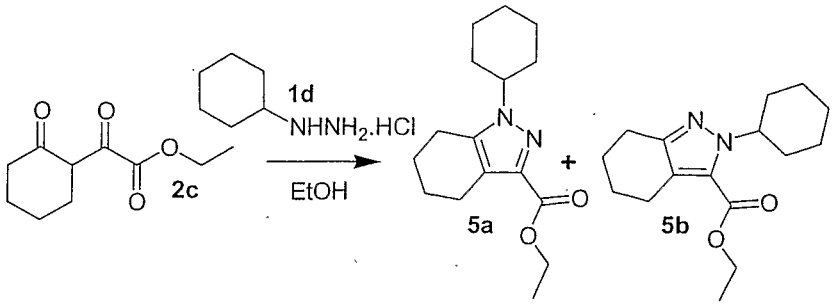


Compound **176** was prepared according to the procedure of Example 2; replacing Compound **2d** with cyclohexyl-hydrazine Compound **5a** and using 2-amino-1-(4-methoxy-phenyl)-ethanone as Compound **2i**). $NaBH_4$ (sodium borohydride) (0.05 g, 1.25 mMol) was added in one portion to a solution of Compound **176** (0.08 g, 0.2 mMol) in MeOH (2 mL) and THF (8 mL) at r.t. The mixture was stirred at r.t. for 4 hrs and the solvent was removed *in vacuo*. The residue was extracted with CH_2Cl_2 and the organic layer was washed successively with water, saturated aqueous $NaHCO_3$ and brine. The organic layer was separated, then dried with anhydrous sodium sulfate and filtered. The solvent was evaporated to provide a crude product which was then purified by preparative TLC on silica gel (3:2 hexane/EtOAc, Rf = 0.35) to provide Compound **241** (29.8 mg, 75%) as a sticky solid.

MS *m/z* 420 (M+Na, 30%), 380 ($M-H_2O$, 100%); ^1H NMR (300 MHZ, $CDCl_3$) δ 7.25 (br s, 1H), 7.21 (d, J = 6.0 Hz, 2H), 6.78 (d, J = 6.0 Hz, 2H), 4.75-4.83 (m, 1H), 3.82-3.98 (m, 1H), 3.71 (s, 3H), 3.55-3.68 (m, 1H), 3.33-3.47 (m, 1H), 2.70 (br t, 2 H), 2.48 (br t, 2 H), 1.58-1.90 (m, 10H), 1.18-1.39 (m, 4H).

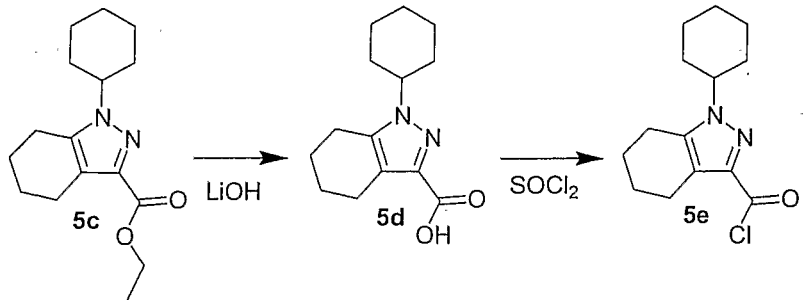
Example 5

1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid cyclohexylmethylamide (Cpd **304**)



For this example, Compound **2c** was prepared as follows: LHMDS (100 mL of 1.0 M solution in THF) was added to a 500 mL round bottom flask and cooled to ⁻78 °C. Cyclohexanone Compound **2a** (10.36 mL, 100 mMol) in 20 mL THF was added dropwise and the mixture was stirred at ⁻78 °C for 1 hr. Diethyl oxalate Compound **2b** (13.6 mL, 100 mMol) was added slowly at ⁻78 °C and the mixture was stirred at the same temperature for 1 hr. The reaction mixture was stirred and allowed to warm to r.t. overnight. The mixture was then concentrated and taken up in EtOAc (500 mL) and washed with 1N HCl (2 × 200 mL) followed by water (2 × 200 mL). The organic layer was separated, then dried with anhydrous sodium sulfate and filtered. The organic layer was separated, then dried with anhydrous sodium sulfate and filtered. The solvent was evaporated to provide an ester Compound **2c** (15 g, 75.7%) as an orange oil.

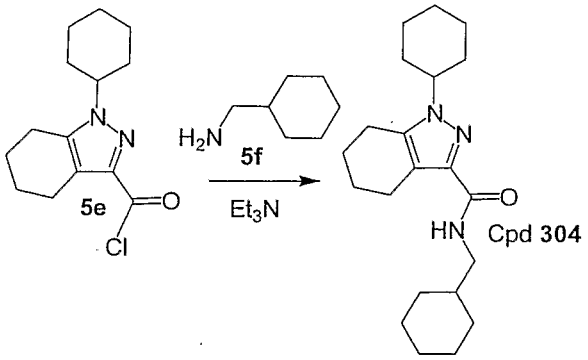
Compound **2c** (1.98 g, 10 mMol) was taken up in EtOH (40 mL) and anhydrous cyclohexyl hydrazine hydrochloride Compound **1d** (1.5 g, 10 mMol) and K_2CO_3 (1.38 g, 10 mMol) were added. The mixture was stirred at r.t. overnight, then filtered and washed with EtOH (20 mL). The combined filtrate was concentrated and purified on a silica gel column (eluted with 20% EtOAc in hexane) to give of a mixture of a major isomer Compound **5b** and a minor isomer Compound **5c** (2.3 g, 83%).



The major isomer Compound **5b** (0.81g, 2.92 mMol) was dissolved in a

solution of MeOH (24 mL) and THF (8 mL) and aqueous LiOH (0.52 g LiOH in 8 mL H_2O) was added. The mixture was stirred at r.t. for 4 hrs, then concentrated and diluted with water (100 mL). The resulting aqueous solution was washed with EtOAc in hexane (1:1 in 50 mL). The aqueous layer was acidified to pH 4 using 1N HCl and extracted with EtOAc (100 mL). The organic layer was separated, then dried over magnesium sulfate and filtered. The solvent was evaporated to provide an acid Compound **5d** (0.7 g, 96%).

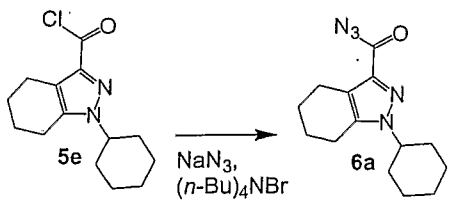
Compound **5d** (0.4 g, 1.6 mMol) was dissolved in 10 mL CH_2Cl_2 (methylene chloride) and was treated with $SOCl_2$ (thionyl chloride) (0.3 mL). The resulting solution was heated to reflux for 3 hrs and the solvent was removed *in vacuo* to provide 0.36 g (84%) of the acid chloride Compound **5e**.



The acid chloride Compound **5e** (0.08 g, 0.3 mMol) was added to a solution of cyclohexylmethylamine Compound **5f** (0.08 mL , 0.6 mMol) in 2 mL of CH_2Cl_2 and triethylamine (0.125 mL, 0.9 mMol). The resulting suspension was stirred at r.t. for 2 hrs and then diluted with 10 mL CH_2Cl_2. The resulting mixture was washed with 1N HCl (2 ×10 mL) and water (2 ×10 mL). The organic layer was dried over sodium sulfate, then concentrated and purified on a silica gel column (eluted with 20% EtOAc in hexane) to provide an amide Compound **304** (90 mg, 88%). MS *m/z* 344 (MH^+).

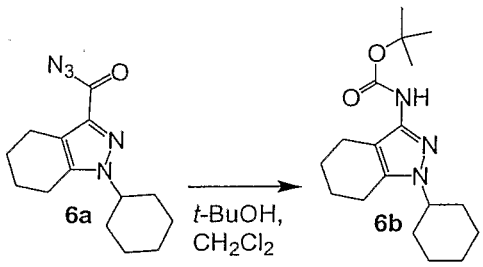
Example 6

naphthalene-2-carboxylic acid (1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-amide (Cpd **178**)

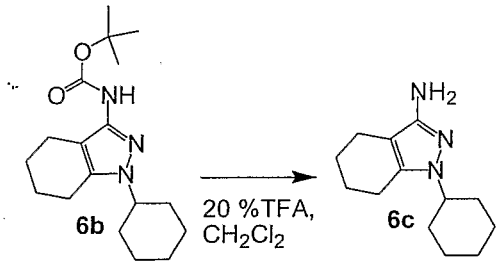


Tetrabutylammonium bromide ($(n\text{-}Bu)_4NBr$) (10 mg) in a catalytic amount was

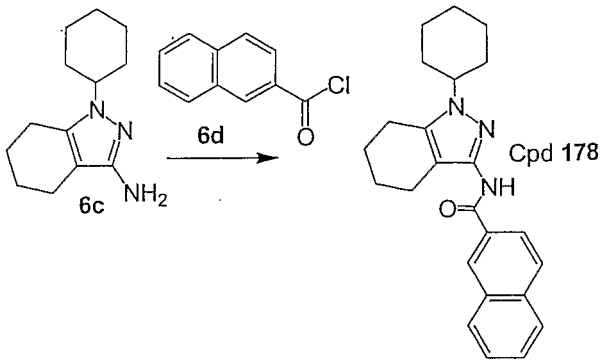
added to a solution of 1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carbonyl chloride Compound **5e** (0.134 g, 0.5 mMol) in DCE (dichloroethane) (5 mL) at 0°C. NaN_3 (sodium azide) (0.5 mL saturated solution in water) was then added dropwise at 0°C. The resulting reaction mixture was stirred for 0.5 hrs before being diluted with cold water and CH_2Cl_2. The organic layer was washed with water (2 × 10 mL), brine (2 × 10 mL), dried over sodium sulfate, filtered and concentrated to give an azide Compound **6a** (0.11 g, 80%).



To a solution of azide Compound **6a** (0.2 g, 0.73 mMol) in 5 mL CH_2Cl_2 was added *t*-BuOH (*tert*-butanol) (1 g, 13.5 mMol). The resulting mixture was refluxed for 48 hrs before being concentrated. The crude product was purified on a silica gel column (eluted with 10% EtOAc in hexane) to give a Boc-protected amine Compound **6b** (0.15 g, 64%).



To a solution of Compound **6b** (0.15 g, 0.47 mMol) in 8 mL CH_2Cl_2 was added 2 mL TFA. The reaction mixture was stirred overnight and then concentrated. The crude product was dissolved in CH_2Cl_2 and washed with 1N NaOH (2 × 20 mL) and water (2 × 20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to give Compound **6c** (0.127 g, 93%).

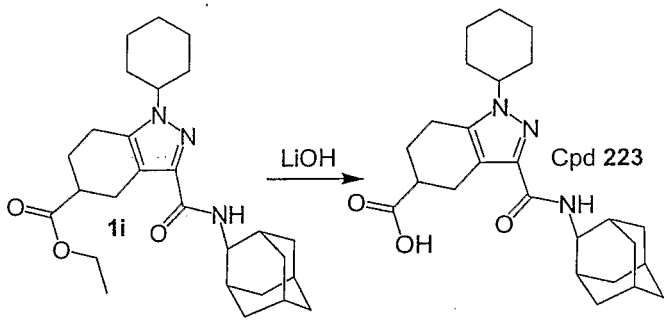


Naphthalene-2-carbonyl chloride Compound **6d** (5 mg, 0.026 mMol) and TEA (0.01 mL, 0.072 mMol) were added to a solution of Compound **6c** (5 mg, 0.023 mMol). The reaction mixture was stirred at r.t. for 4 hrs, then concentrated and purified on a silica gel column (eluted with 15% EtOAc in hexane) to give Compound **178** (5.1 mg, 60%). MS *m/z* 374 (MH^+)

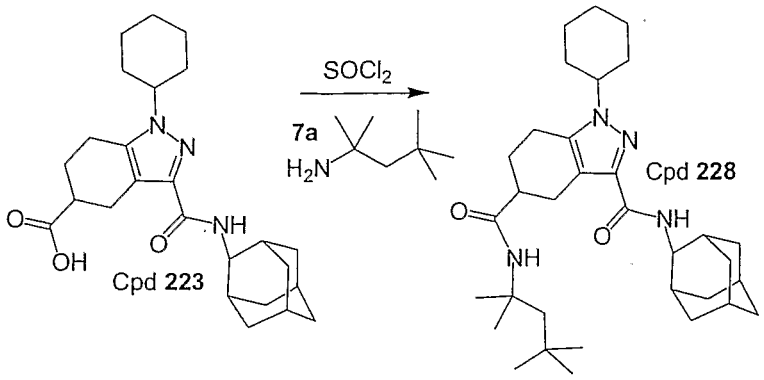
Example 7

3-(adamantan-2-ylcarbamoyl)-1-cyclohexyl-4,5,6,7-tetrahydro-1*H*-indazole-5-carboxylic acid (Cpd **223**)

1-cyclohexyl-4,5,6,7-tetrahydro-1*H*-indazole-3,5-dicarboxylic acid 3-adamantan-2-ylamide 5-[(1,1,3,3-tetramethyl-butyl)-amide] (Cpd **228**)



The 3-(adamantan-2-ylcarbamoyl)-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-5-carboxylic acid ethyl ester Compound **1i** (100 mg, 0.22 mMol) was added to a solution of LiOH (lithium hydroxide) monohydrate (46 mg) in a 3:1:1 ratio of THF:MeOH:water (10 mL). The mixture was stirred overnight at r.t. and then concentrated *in vacuo*. The residue was neutralized with 1N HCl to give Compound **223** (87 mg, 93%) as a white precipitate. MS *m/z* 426 $(M+H)^+$, 448 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.26 (1H, b), 4.21 (1H, m), 3.91 (1H, m), 3.31 (1H, m), 2.93 (1H, m), 2.75 (3H, m), 2.21 (1H, m), 1.88 (23H, m), 1.35 (2H, m).



Thionyl chloride (1 mL) was added to Compound **223** (10 mg, 0.023 mMol) and the mixture was refluxed for 10 min. The excess thionyl chloride was evaporated and the residue was washed with CH_2Cl_2. 1,1,3,3-tetramethyl-butylamine Compound **7a** (6 mg, 0.046 mMol) was added to the residue in CH_2Cl_2 and the mixture was stirred for 70 min, washed with 1N HCl and brine, then dried over sodium sulfate. The crude product was purified by preparative TLC (50% EtOAc in hexane) to give Compound **228** (8 mg, 63.5%) as a white solid.

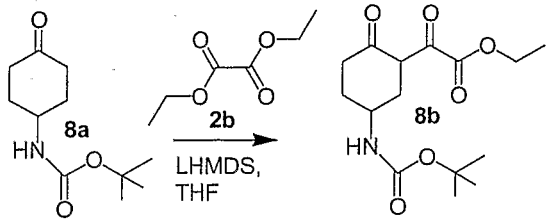
MS *m/z* 537 $(M+H)^+$, 559 $(M+Na)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.26 (1H, b), 5.42 (1H, b), 4.19 (1H, m), 3.90 (1H, m), 3.21 (1H, m), 2.79 (2H, m), 2.56 (2H, m), 2.21 (1H, m), 1.7-2.1 (23H, m), 1.42 (4H, m), 1.19 (3H, s), 1.02 (9H, s), 0.97 (3H, s).

Example 8

[1-cyclohexyl-3-(1,3,3-trimethyl-bicyclo[2.2.1]hept-2-ylcarbamoyl)-4,5,6,7-tetrahydro-1H-indazol-5-yl]-carbamic acid tert-butyl ester (Cpd **86**)

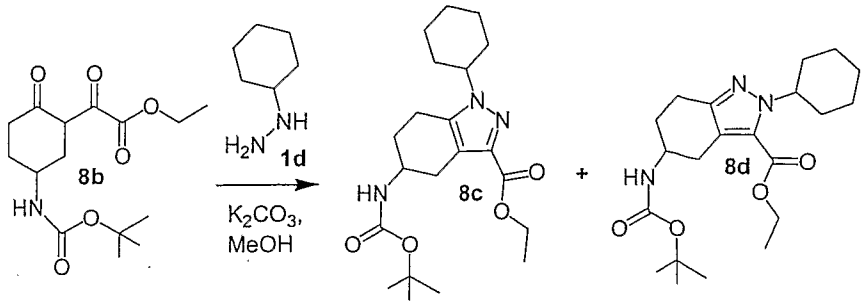
5-amino-1-cyclohexyl-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylic acid (1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide (Cpd **92**)

1-cyclohexyl-5-hydroxy-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide (Cpd **93**)

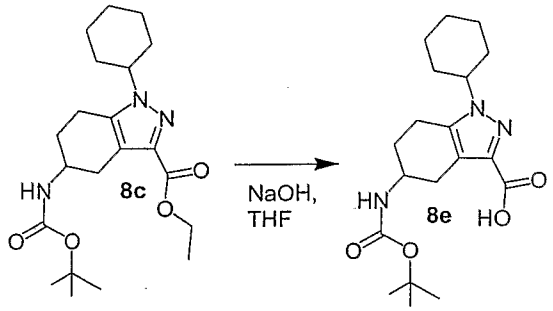


According to the procedure of Example 2, a solution of (4-oxo-cyclohexyl)-carbamic acid tert-butyl ester Compound **8a** in ether was used in place of cyclohexanone Compound **2a** and carried forward to produce (5-tert-

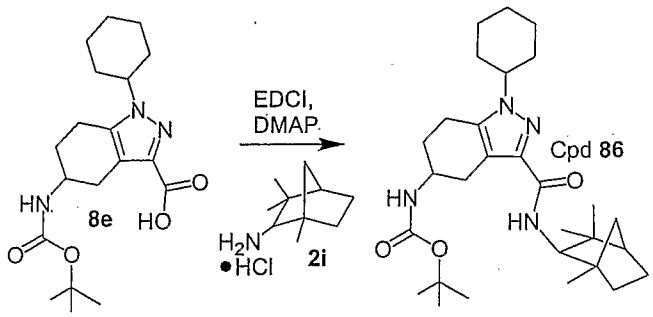
butoxycarbonylamino-2-oxo-cyclohexyl)-oxo-acetic acid ethyl ester Compound **8b**.



Using the procedure of Example 2, Compound **8b** was used in place of oxo-(2-oxo-cyclohexyl)-acetic acid ethyl ester Compound **2c** and cyclohexyl-hydrazine Compound **1d** was used in place of benzylhydrazine dihydrochloride Compound **2d** to produce a major isomer 5-tert-butoxycarbonylamino-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester Compound **8c** and a minor isomer 5-tert-butoxycarbonylamino-2-cyclohexyl-4,5,6,7-tetrahydro-2H-indazole-3-carboxylic acid ethyl ester Compound **8d**.

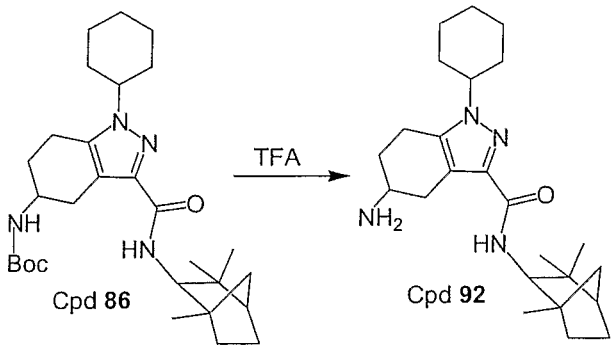


Using the procedure of Example 2, Compound **8c** was used in place of 1-benzyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester Compound **2e** to produce 5-tert-butoxycarbonylamino-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid Compound **8e**.



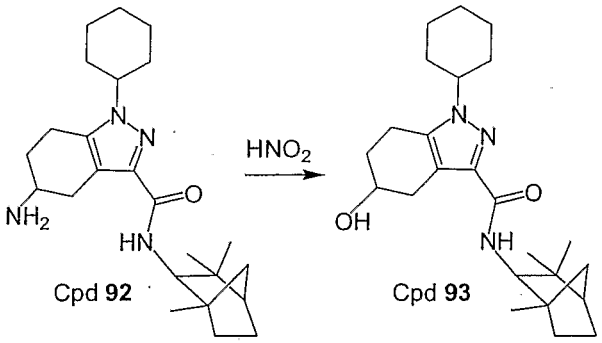
Using the procedure of Example 24, Compound **8e** was used in place of 1-

cyclohexyl-7-hydroxy-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid Compound **24a** and 1,3,3-trimethyl-bicyclo[2.2.1]hept-2-ylamine hydrochloride Compound **2i** was used in place of (2*S*,3*R*)-3-amino-bicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester Compound **24b** to produce Compound **86**.



Ester Compound **86** (0.1 g, 0.2 mMol) was added to a solution of 50% TFA in CH_2Cl_2 (2 mL). The mixture was stirred for 3 hrs and the solvent was evaporated to give Compound **92** (0.1 g, yield 98%) as a TFA salt.

MS *m/z* 399 $(M+H)^+$, 421 $(M+Na)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.05 (1H, b), 6.03 (3H, b), 3.86 (1H, m), 3.64 (1H, m), 3.42 (1H, m), 2.89 (2H, m), 2.69 (1H, m), 2.36 (1H, m), 1.65-1.95 (11H, m), 1.18-1.41 (8H, m), 1.05 (3H, s), 1.02 (3H, s), 0.82 (3H, s).



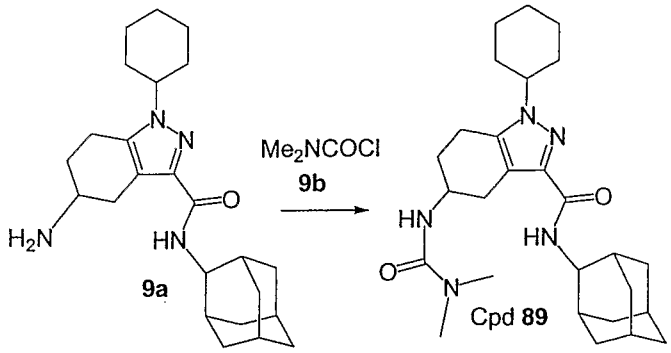
Compound **92** (0.1 g, 0.2 mMol) was added to a solution of $NaNO_2$ (27 mg, 0.4 mMol) in acetic acid (3 mL) at 0 °C. The mixture was stirred for 2 hrs and the product was run on prep TLC (30% EtOAc in hexane) to give Compound **93** (22 mg, yield 28%).

MS *m/z* 400 $(M+H)^+$, 422 $(M+Na)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.02 (1H, b), 4.19 (1H, m), 3.90 (1H, m), 3.72 (1H, m), 3.19 (1H, m), 2.81 (3H, m), 2.61 (1H, m), 1.89 (7H, m), 1.70 (4H, m), 1.34 (4H, m), 1.21 (3H, m), 1.13(3H, s), 1.09 (3H, s), 0.82

"(3H, s)."

Example 9

1-cyclohexyl-5-(3,3-dimethyl-ureido)-4,5,6,7-tetrahydro-1*H*-indazole-3-carboxylic acid adamantan-2-ylamide (Cpd **89**)

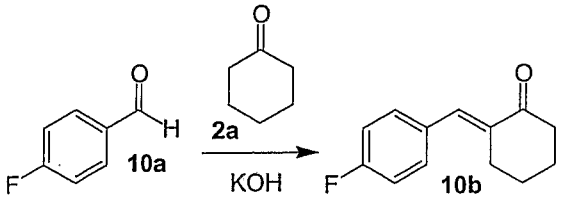


Dimethylcarbamyl chloride Compound **9b** (0.56 mL, 6 mMol) was added dropwise to a solution of Compound **9a** (0.8 g, 2 mMol) (prepared similarly to Compound **92** using the procedure of Example 8) and TEA (0.3 g, 3 mMol) in CH_2Cl_2 (10 mL). The mixture was stirred for 2 hrs and the reaction was quenched with 1N NaOH. The organic layer was dried over Na_2SO_4 and the CH_2Cl_2 was evaporated. The crude product was purified via column chromatography (using EtOAc as the eluent) to give Compound **89** (0.8 g, yield 86%) as a white solid.

MS *m/z* 468 $(M+H)^+$, 490 $(M+Na)^+$. ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.26 (1H, b), 4.32 (1H, d, J = 6.6 Hz), 4.19 (1H, m), 4.07 (1H, m), 3.92 (1H, m), 3.21 (1H, dd, J = 16.0, 5.2 Hz), 2.88 (6H, s), 2.65 (2H, m), 2.15 (1H, m), 2.02 (2H, m), 1.90 (16H, m), 1.75 (6H, m), 1.32 (2H, m).

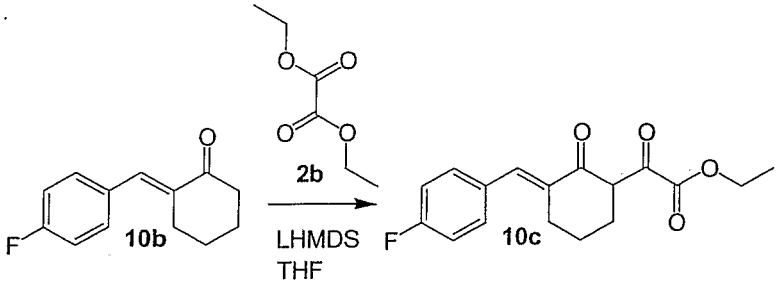
Example 10

1-(2,4-dichloro-phenyl)-7-(4-fluoro-benzylidene)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid piperidin-1-ylamide (Cpd **297**)

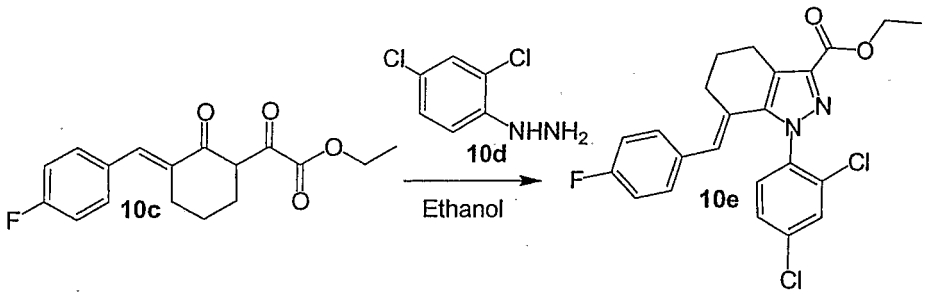


An aqueous KOH (0.25 g in 4.4 mL water) solution was added to p-fluorobenzaldehyde Compound **10a** (1.04 mL, 10 mMol) and the mixture was heated to 65 °C. Cyclohexanone Compound **2a** (1.03 mL, 10 mMol) was added dropwise over 10 min and the reaction mixture was refluxed for 5 hrs, then cooled to r.t. and stirred at

r.t. overnight. The reaction mixture was acidified with 1N HCl (26 mL) and diluted with EtOAc. The organic layer was separated and washed with brine, then dried with anhydrous sodium sulfate and filtered. The solvent was evaporated to provide a crude product which was then purified by silica gel column (eluted with 6% EtOAc in hexane) to give 2-(4-fluoro-benzylidene)-cyclohexanone Compound **10b** (1.1 g, 54%).

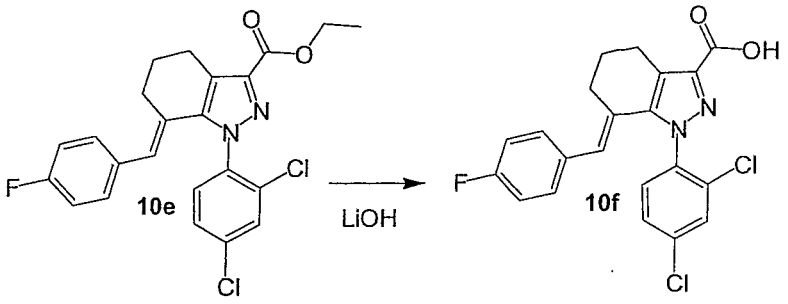


Cyclohexanone Compound **10b** (1.1 g, 5.4 mMol) in THF (5 mL) was added dropwise to a solution of lithium bis(trimethylsilyl)amide (5.4 mL of 1.0M solution in THF) in THF (10 mL) at -78 °C. The mixture was stirred at -78 °C for 1 hr, then diethyl oxalate Compound **2b** (0.732 mL, 5.4 mMol) in THF (5 mL) was added slowly at -78 °C. The mixture was stirred at -78 °C for 1 hr, then stirred and allowed to warm to r.t. overnight. The mixture was concentrated, taken up in EtOAc (100 mL) and washed with 1N HCl (2×50 mL) and water (2×50 mL). The organic layer was separated, then dried with anhydrous sodium sulfate and filtered. The solvent was evaporated to provide a [3-(4-fluoro-benzylidene)-2-oxo-cyclohexyl]-oxo-acetic acid ethyl ester Compound **10c** (1.4 g, 85%) as an orange oil which was used in the next step without further purification.



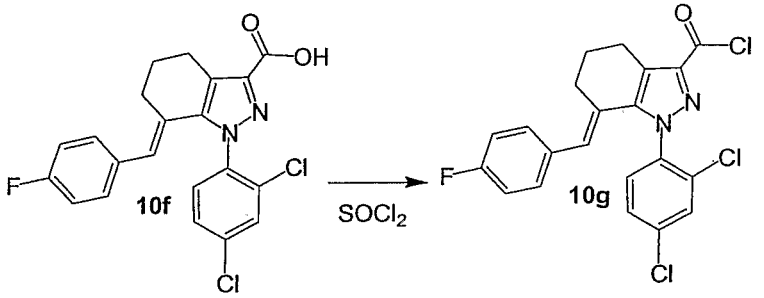
Compound **10c** (1.4 g, 4.62mmol) was taken up in ethanol (30 mL), then anhydrous (2,4-dichloro-phenyl)-hydrazine hydrochloride Compound **10d** (0.99 g, 4.62 mMol) and K_2CO_3 (1.28 g, 9.24 mMol) were added. The reaction mixture was stirred at r.t. overnight, then filtered and washed with ethanol (20 mL). The combined filtrate was concentrated and purified on a silica gel column (eluted with 20% EtOAc in

hexane) to give 1-(2,4-Dichloro-phenyl)-7-(4-fluoro-benzylidene)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester Compound **10e** (0.8 g, 39%).

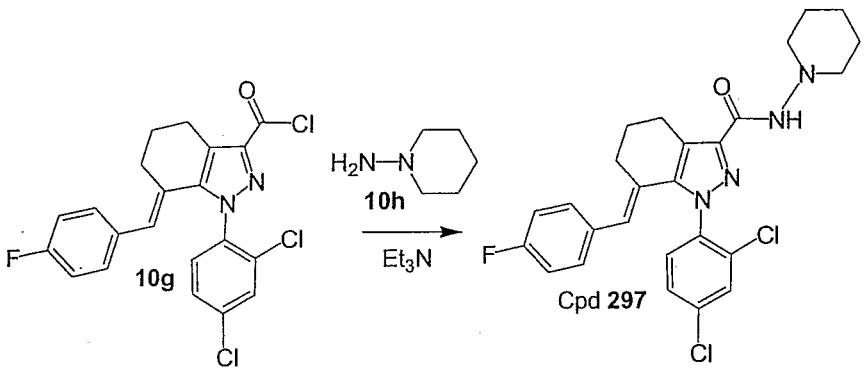


Ethyl ester Compound **10e** (0.8 g, 1.8 mMol) was dissolved in THF (18 mL). Aqueous LiOH (lithium hydroxide) (0.26 g in 6 mL), then ethanol (2 mL) were added and the mixture was stirred at r.t. for 24 hrs, then concentrated, diluted with water (25 mL) and acidified to pH 4 using 1N HCl. The aqueous suspension was extracted with EtOAc (100 mL).

The organic layer was separated and washed with brine, then dried over magnesium sulfate and filtered. The solvent was evaporated to provide an acid Compound **10f** (0.74 g, 98%).



The acid Compound **10f** (0.74 g, 1.77 mMol) was taken up in CH_2Cl_2 (5 mL), then treated with thionyl chloride (1 mL, 14.1 mMol). The solution was heated to reflux for 3 hrs, the solvent was removed *in vacuo* to obtain the acid chloride Compound **10g** (0.76 g, 99%).



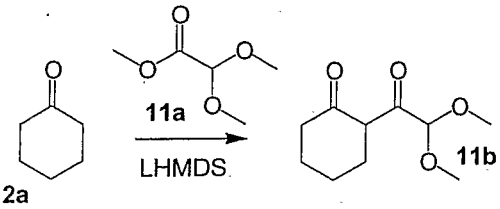
Compound **10g** (0.044 g, 0.1 mMol) was added to a solution of commercially available 1-aminopiperidine Compound **10h** (0.021 mL, 0.2 mMol) in CH_2Cl_2 (2 mL) and triethylamine (0.055 mL, 0.4 mMol). The suspension was stirred, then diluted and washed. The organic layer was dried, concentrated and purified on a silica gel column (eluted with 40% EtOAc in hexane) to provide Compound **297** (40 mg, 80.2%). MS *m/z* 499 (MH^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57-7.41 (m, 4H), 7.07-6.92 (m, 4H), 5.89 (s, 1H), 3.09-3.00(m, 2H), 2.87-2.79 (m, 4H), 2.71-2.54 (m, 2H), 1.93-1.68 (m, 6H), 1.45-1.36 (m, 2H).

Compound **297** (100 mg, 0.2 mMol) was dissolved in CH_2Cl_2 (2 mL) and a solution of 1N HCl in ether (1 mL) was added slowly. The mixture was stirred at r.t. for 1 hr, then concentrated and washed with ether (3X). The remaining ether was removed *in vacuo* to provide Compound **297** (95 mg, 89%) as a hydrochloride salt.

MS *m/z* 499 (MH+); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.33(s, 1H), 7.57(s, 1H), 7.46(s, 2H), 7.06-6.93 (m, 4H), 5.93 (s, 1H), 4.20-3.61(broad peak, 4H), 3.02-2.88 (m, 2H), 2.78-2.52 (m, 2H), 2.21-1.55 (m, 8H).

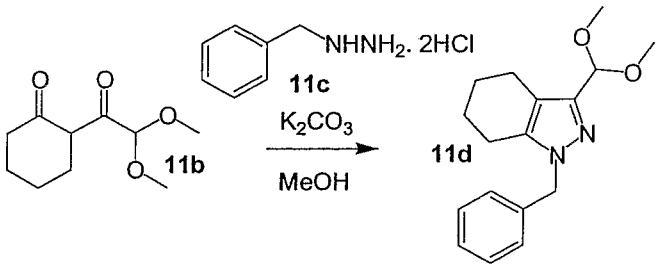
Example 11

2-(1-benzyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-ethenesulfonic acid [(1*R*)-1-phenyl-ethyl]-amide (Cpd **260**)

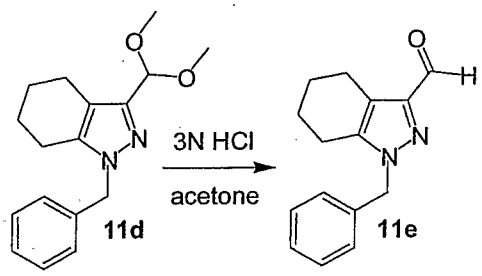


Cyclohexanone Compound **2a** (1.37 g, 14.0 mMol) in THF (5 mL) was added dropwise to a solution of LHMDS (16.0 mL, 16.0 mMol) in anhydrous THF (25 mL) at –78 °C under a N_2 atmosphere. The solution was stirred at –78 °C for about 1 hr. Methyl dimethoxyacetate Compound **11a** (1.88 g, 14.0 mMol) in anhydrous THF (5

mL) was then added dropwise. The reaction mixture was stirred while warming to r.t. over a period of about 15 hrs, then the reaction was quenched with water (5 mL). The organic layer was diluted with EtOAc (100 mL) and washed with water and brine. The organic layer was separated and dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude product as an oil. The oil was purified by flash chromatography (eluted with 10% EtOAc in hexane) to afford 2-(2,2-dimethoxy-acetyl)-cyclohexanone Compound **11b** (1.82 g, 65%).

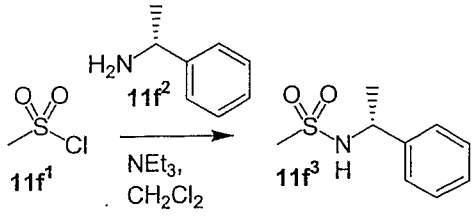


Benzylhydrazine dihydrochloride Compound **11c** (1.75 g, 9.00 mMol) and K_2CO_3 (1.51 g, 10.92 mMol) were added to a solution of Compound **11b** (1.80 g, 9.10 mMol) in MeOH (50 mL) at 0 °C under a N_2 atmosphere. The reaction mixture was stirred overnight while warming to r.t., then the reaction was quenched with water (20 mL). The organic layer was diluted with EtOAc (200 mL) and washed with water and brine. The organic layer was separated and dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude product as an oil. The oil was purified by flash chromatography (eluted with 20% EtOAc in hexane) to afford 1-benzyl-3-dimethoxymethyl-4,5,6,7-tetrahydro-1H-indazole Compound **11d** (1.80 g, 70%) as a colorless oil.

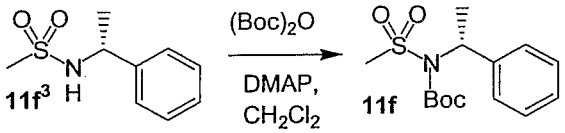


3N HCl (8 mL) was added to a solution of Compound **11d** (1.70 g, 5.9 mMol) in acetone (50 mL) at 0 °C under a N_2 atmosphere. The reaction mixture was stirred for 4 hrs while warming to r.t., then the reaction was quenched with water (20 mL), neutralized to pH 7 with K_2CO_3 and diluted with CH_2Cl_2 (100 mL). The organic layer was washed with water and brine, separated and dried with anhydrous sodium sulfate,

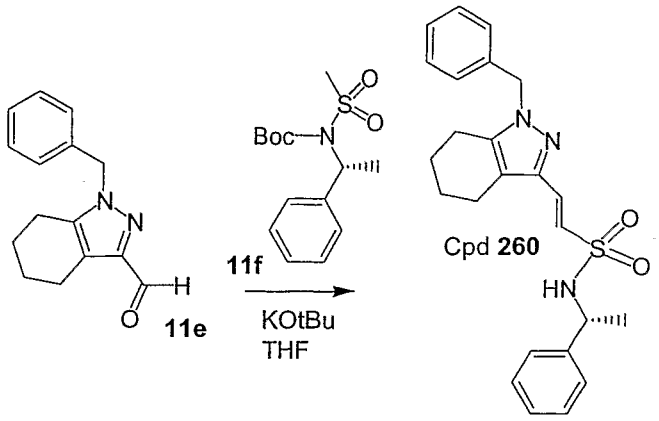
then filtered and concentrated *in vacuo* to afford a 1-benzyl-4,5,6,7-tetrahydro-1H-indazole-3-carbaldehyde Compound **11e** (1.35 g, 95%) as a colorless oil.



Methanesulfonyl chloride Compound **11f**[1] (2.0 g, 17 mMol) and TEA (2.43 mL, 17.46 mMol) were added to a solution of (1*R*)-1-phenyl-ethylamine Compound **11f**[2] (1.75 g, 17.5 mMol) in CH_2Cl_2 (50 mL) at 0°C under a N_2 atmosphere. The mixture was stirred for 3 hrs while warming to r.t., then the reaction was quenched with water (5 mL). The organic layer was diluted with CH_2Cl_2 (100 mL) and then washed with water and brine. The organic layer was separated, dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to afford the corresponding N-(1-phenyl-ethyl)-methanesulfonamide Compound **11f**[3] as an oil.



$(Boc)_2O$ (di-*tert*-butyldicarbonate) (4.57 g, 21.0 mMol) and DMAP (8 mg) were added to a solution of the methanesulfonamide Compound **11f**[3] in CH_2Cl_2 (10 mL) at 0 °C under a N_2 atmosphere. The mixture was stirred overnight while warming to r.t., then the reaction was quenched with a saturated solution of $NaHCO_3$ (sodium bicarbonate) (10 mL). The organic layer was diluted with CH_2Cl_2 (100 mL) and then washed with water and brine. The organic layer was separated, dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude Boc-protected methanesulfonamide product. The product was purified by flash chromatography (eluted with 10% EtOAc in hexane) to afford (methylsulfonyl)[(1*R*)-1-phenyl-ethyl]-carbamic acid tert-butyl ester Compound **11f** (3.89 g, 80%) as a colorless oil.

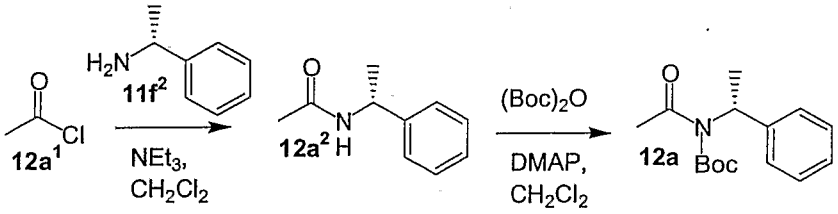


Adapting a published procedure (Tozer MJ, Woolford AJA and Linney IA, *Synlett,* **1998**, *2*, 186-188) to obtain the target compound, a 1M solution of KOtBu (potassium tert-butoxide) in THF (0.75 mL, 0.75 mMol) was added dropwise to a solution of the ester Compound **11f** (0.070 g, 0.250 mMol) in anhydrous THF (5 mL) at –78 °C under a N_2 atmosphere. After 45 min, Compound **11e** (0.060 g, 0.250 mMol) diluted in THF (3 mL) was added dropwise. The solution was reacted over a 15 hr period while warming to ambient temperature. The reaction was quenched with water (5 mL). The organic layer was diluted with EtOAc (100 mL) and then washed with water and brine. The organic layer was separated and dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude product. The product was purified by flash chromatography (eluted with 20% EtOAc in hexane) to give Compound **260** (0.079 g (75%), as a white solid.

MS *m/z* 422 (MH^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, J = 15.5 Hz, 1H), 7.35-7.19 (m, 8H), 7.11-7.09 (m, 2H), 6.42 (d, J = 15.5 Hz, 1H), 5.21 (s, 2H), 4.61-4.11 (m, 2H), 2.45-2.41 (m, 2H), 2.36-2.33 (m, 2H), 1.75-1.67 (m, 4H), 1.55 (d, J = 6.5 Hz, 3H).

Example 12

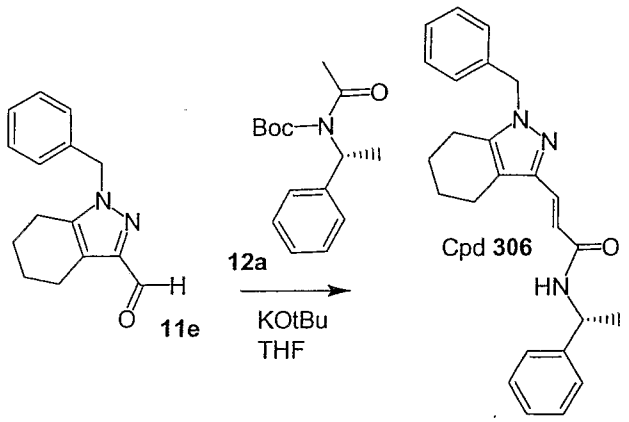
3-(1-benzyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-N-[(1*R*)-1-phenyl-ethyl]-acrylamide (Cpd **306**)



Acetyl-(1-phenyl-ethyl)-carbamic acid tert-butyl ester Compound **12a** was synthesized using the procedure of Example 12, replacing mesyl chloride Compound

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11f with acetyl chloride Compound **12a**[1].

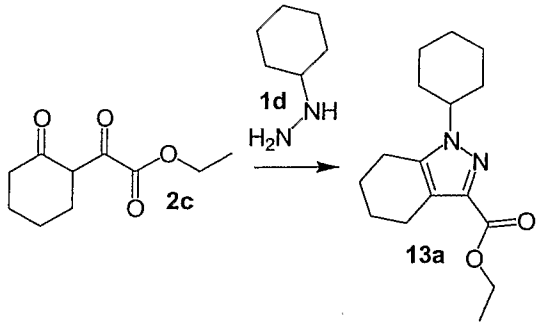


Acetyl-(1-phenyl-ethyl)-carbamic acid tert-butyl ester Compound **11e** was reacted with Compound **12a**, using the procedure of Example 12, to afford Compound **306** (0.067 g, 70%) as a white solid.

MS *m/z* 386 (MH^+) ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (d, J = 15.8 Hz, 1H), 7.35-7.23 (m, 8H), 7.11-7.09 (m, 2H), 6.42 (d, J = 15.8 Hz, 1H), 5.77-5.11 (d, J = 7.4 Hz, 1H), 5.30-5.23 (m, 1H), 5.21 (s, 2H), 2.59-2.56 (m, 2H), 2.44-2.42 (m, 2H), 1.74-1.71 (m, 4H), 1.54 (d, J = 6.9 Hz, 3H).

Example 13

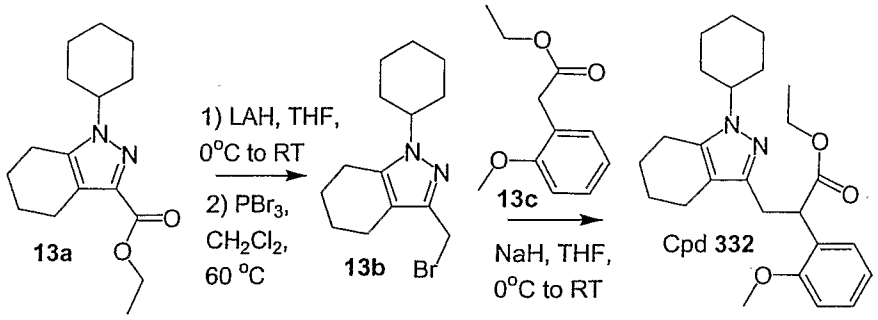
3-(1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-2-(2-methoxy-phenyl)-propionic acid ethyl ester (Cpd **332**)



Cyclohexylhydrazine hydrochloride Compound **1d** (6.0 g, 46.5 mMol) and K_2CO_3 (9.0 g, 65.0 mMol) were added to a solution of Compound **2c** (10.10 g, 50.95 mMol) in EtOH (50 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred overnight, concentrated to dryness, then diluted with water (100 mL) and EtOAc (500 mL). The organic layer was washed with brine, separated, dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (eluted with 10% EtOAc in hexane) afforded 1-

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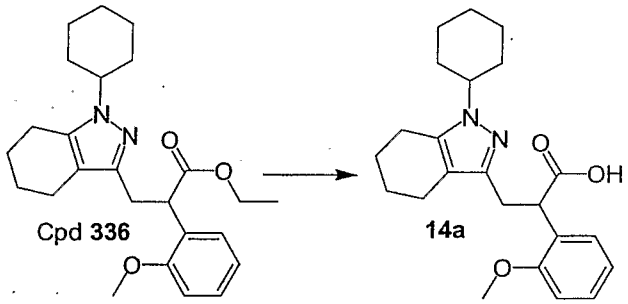
cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester Compound **13a** (12.2 g, 44.14 mMol, 95%) as a yellow oil.



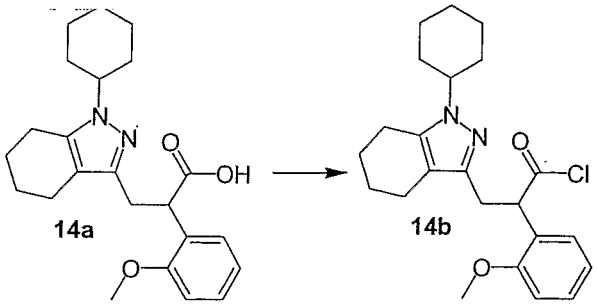
The scheme above, wherein Compound **13a** is taken to Compound **332** using the conditions and reagents indicated, describes the use of a published procedure (Murray WV, Hadden SK, Wachter MP, *J. Het. Chem.*, **1990**, 27, 1933-40; US Patent 4,826,868; US Patent 4,898,952; US Patent 5,051,518; US Patent 5,164,381 and US Patent 5,242,940) to produce the target Compound **332**. MS *m/z* 411 (MH^+).

Example 14

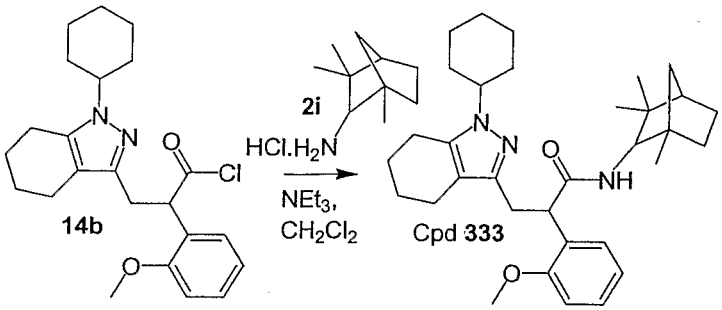
3-(1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-2-(2-methoxy-phenyl)-N-(1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-propionamide (Cpd **333**)



Using the procedure of Example 2, 1N NaOH (10 mL) was added to a solution of ester Compound **336** (0.295 g, 0.72 mMol) in THF (10 mL). The mixture was stirred for 30 hrs, acidified to pH 2 with 1N HCl and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over sodium sulfate, then filtered and concentrated *in vacuo* to yield a carboxylic acid Compound **14a** (0.150 g, 54%) as a white solid.



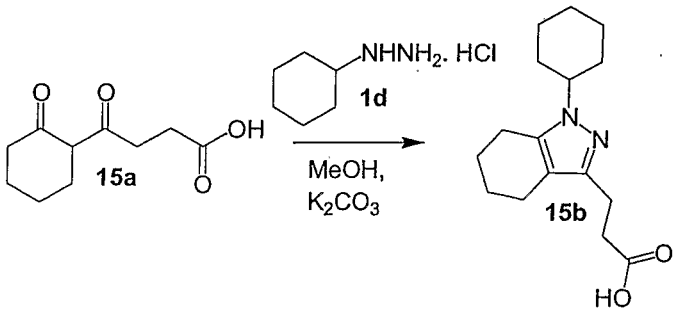
Thionyl chloride (0.25 g, 2.16 mMol) was added to a solution of Compound **14a** (0.15 g, 0.39 mMol) in CH_2Cl_2 (10 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred for 3 hrs and concentrated *in vacuo* to afford Compound **14b**.



Triethylamine (0.16 g, 1.58 mMol) and Compound **14b** (0.075 g, 0.63 mMol) were added to a solution of Compound **2i** (0.12 g, 0.63 mMol) in CH_2Cl_2 (10 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred at r.t. for 3 hrs, then diluted with water (10 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (eluted with 20% EtOAc in hexane) afforded Compound **333** (0.039 g, 33%) as a white solid. MS *m/z* 518 (MH^+).

Example 15

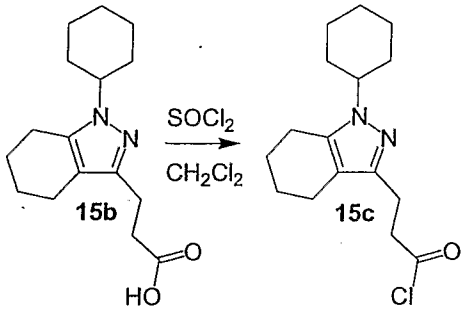
3-(1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-N-(1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-propionamide (Cpd **50**)



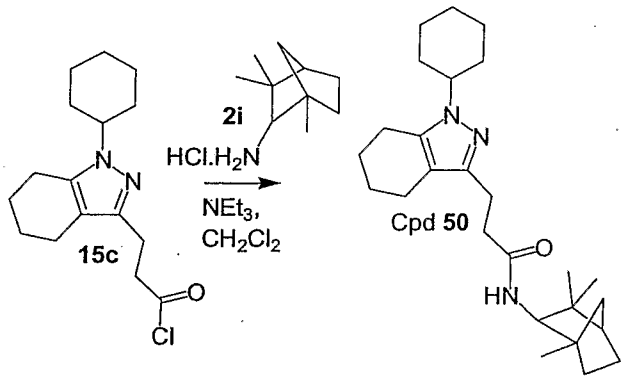
Carboxylic acid Compound **15a** was derived using a published procedure (as described in Murray WV, Wachter MP, Barton D and Forero-Kelly Y, *Synthesis,* **1991**,

PCT Published

01, 18-20) using cyclohexanone as the starting material and carried forward using the procedure of Example 2 to provide 3-(1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-propionic acid Compound **15b**. MS *m/z* 277 (MH^+).



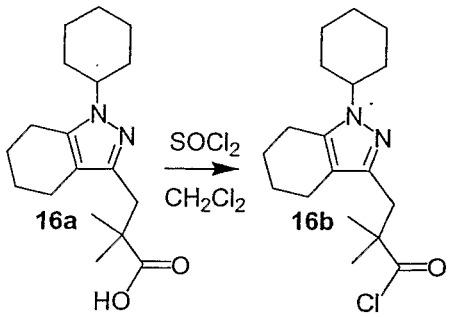
Thionyl chloride (1.94 g, 16.41 mMol) was added to a solution of Compound **15b** (1.51 g, 5.47 mMol) in CH_2Cl_2 (10 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred for 3 hrs and concentrated *in vacuo* to afford the corresponding acid chloride Compound **15c**.



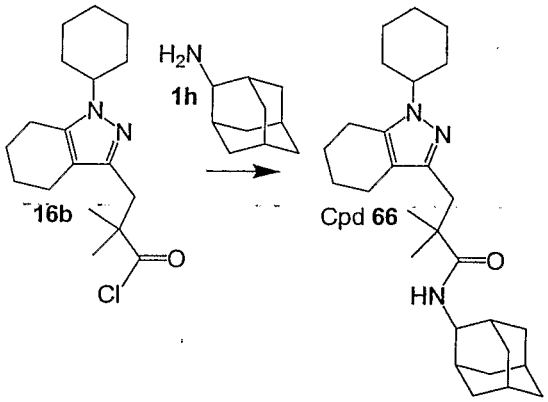
Triethylamine (0.16 g, 1.58 mMol) and acid chloride Compound **15c** (0.15 g, 0.50 mMol) were added to a solution of Compound **2i** (0.08 g, 0.50 mMol) in CH_2Cl_2 (10 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred at r.t. for 3 hrs, then diluted with water (10 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (eluted with 20% EtOAc in hexane) afforded Compound **50** (0.05 g, 24%) as a white solid. MS *m/z* 412 (MH^+).

Example 16

N-adamantan-2-yl-3-(1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-2,2-dimethyl-propionamide (Cpd **66**)



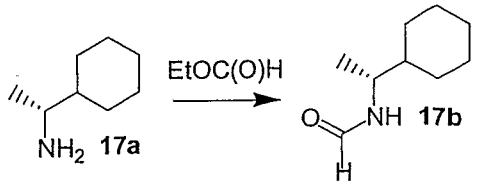
3-(1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-2,2-dimethyl-propionic acid Compound **16a** was derived by the procedure described in US Patent 5,051,518 whereby cyclohexanone Compound **2a** was used as the starting material and carried forward. MS *m/z* 305 (MH^+). Thionyl chloride (0.28 g, 2.40 mMol) was added to a solution of the acid Compound **16a** (0.24 g, 0.80 mMol) in CH_2Cl_2 (5 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred for 3 hrs and concentrated *in vacuo* to afford the corresponding acid chloride Compound **16b**.



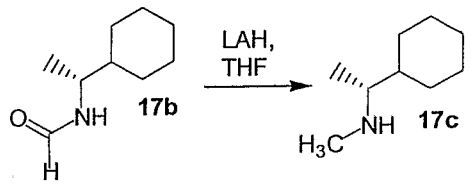
Triethylamine (0.05 g, 0.50 mMol) and acid chloride Compound **16b** (0.70 g, 0.60 mMol) were added to a solution of 2-adamantanamine Compound **1h** (0.03 g, 0.20 mMol) in CH_2Cl_2 (5 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred at r.t. for 3 hrs, then diluted with water (10 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude oil. Purification by flash chromatography (eluted with 20% EtOAc in hexane) afforded Compound **66** (0.032 g, 37%) as a white solid. MS *m/z* 438 (MH^+).

Example 17

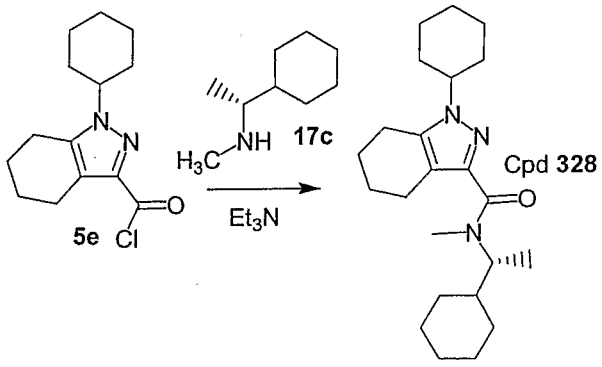
1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid [(1*R*)-1-cyclohexyl-ethyl]-methylamide (Cpd **328**)



Ethyl formate (1.2 mL, 15.0 mMol) was added to a round bottom flask containing (1*R*)-1-cyclohexyl-ethylamine Compound **17a** (1.27 g, 10 mMol) at 0 °C and the mixture was stirred at r.t. for 15 hrs. Excess ethyl formate was removed *in vacuo* to obtain N-[(1*R*)-1-cyclohexyl-ethyl]-formamide Compound **17b** (1.55 g) as a white solid, which was used in the next step without purification. MS *m/z* 156 (MH^+).



A solution of LAH in THF (1.0 M, 15 mL, 15 mMol) was added dropwise via syringe to a solution of Compound **17b** (1.55 g, 10 mMol) in anhydrous THF at 0 °C. The mixture was heated to reflux for 8 hrs and provided a grayish suspension. The suspension was cooled to 0 °C and the reaction was quenched carefully by a sequential addition of water (0.6 mL), 2N NaOH (0.6 mL) and water (2.0 mL). A white residue was produced, then filtered through a sintered glass funnel and washed with Et_2O (20 mL). The solvent from the combined filtrate was removed *in vacuo* to provide [(1*R*)-1-cyclohexyl-ethyl]-methylamine Compound **17c** (1.1 g, 72%) as a pale yellow oil, which was used in the next step without purification. MS *m/z* 142 (MH^+).

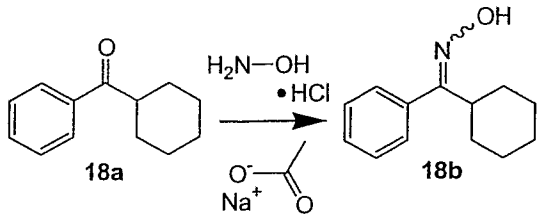


The acid chloride Compound **5e** (0.04 g, 0.15 mMol) was added to a solution of

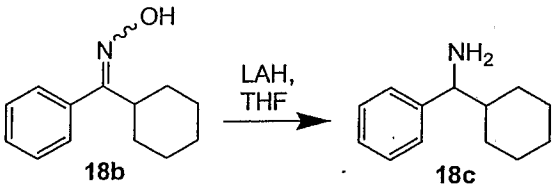
the methylamine Compound **17c** (0.05 g, 0.035 mMol) in CH_2Cl_2 (2 mL) and triethylamine (0.06 mL, 0.5 mMol). The resulting suspension was stirred at r.t. for 2 hrs, diluted with CH_2Cl_2 (10 mL), then washed with 1N HCl (2 ×10 mL) and water (2 ×10 mL). The organic layer was dried over sodium sulfate, then concentrated and purified on a silica gel column (eluted with 20% EtOAc in hexane) to provide Compound **328** (44 mg, 80%). MS *m/z* 372 (MH^+).

Example 18

1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (cyclohexyl-phenyl)methylamide (Cpd **331**)



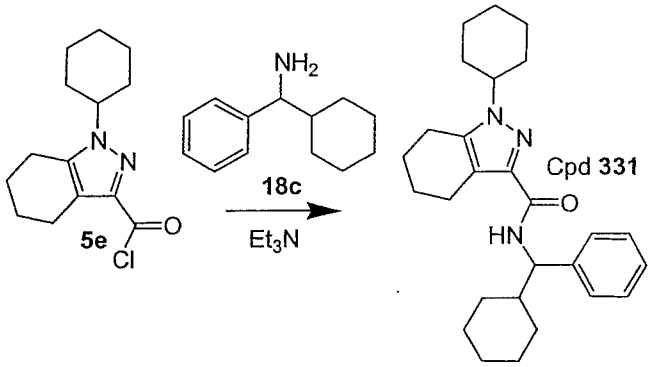
Hydroxylamine hydrochloride (0.48 g, 6.7 mMol) and sodium acetate (1.4 g, 10.2 mMol) were added to a round bottom flask containing cyclohexyl-phenyl-methanone Compound **18a** (0.97 g, 5.1 mMol) in MeOH (30 mL) at r.t. The mixture was stirred at r.t. for 15 hrs. The solvent was removed *in vacuo* and the residue was extracted with CH_2Cl_2. The organic layer was sequentially washed with a saturated solution of $NaHCO_3$, then brine. The organic layer was dried over Na_2SO_4, decanted and the solvent removed *in vacuo* to provide cyclohexyl-phenyl-methanone oxime Compound **18b** (1.0 g) as a white solid, which was used in the next step without purification. MS *m/z* 204 (MH^+).



A solution of Compound **18b** (0.45 g, 0.22 mMol) in anhydrous THF (10 mL) added dropwise via syringe to a suspension of LAH (0.5 g, 1.3 mMol) in THF (20 mL) at 0 °C. The mixture was heated to reflux for 8 hrs and provided a grayish suspension. The suspension was cooled to 0 °C and the reaction was quenched carefully by sequential addition of water (0.5 mL), 2N NaOH (0.5 mL) and water (1.5 mL). A white residue was produced, then filtered through a sintered glass funnel and washed with Et_2O (20 mL). The solvent from the combined filtrate was removed *in vacuo* to

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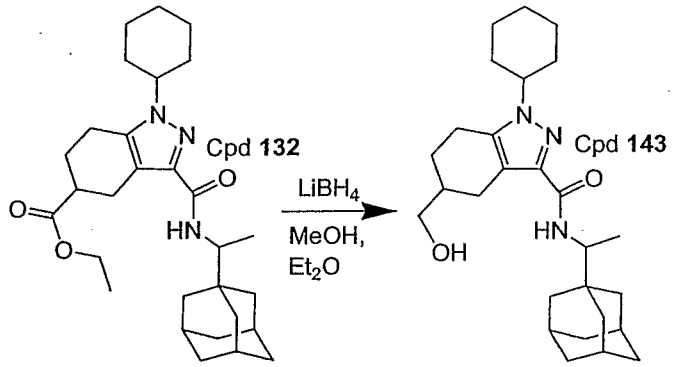
provide C-cyclohexyl-C-phenyl-methylamine Compound **18c** (0.38 g, 91%) as a pale yellow oil, which was used in the next step without purification. MS *m/z* 190 (MH^+).



Using the procedure of Example 5, Compound **18c** was reacted with acid chloride Compound **5e** to provide Compound **331**.

Example 19

1-cyclohexyl-5-hydroxymethyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (1-adamantan-1-yl-ethyl)-amide (Cpd **143**)



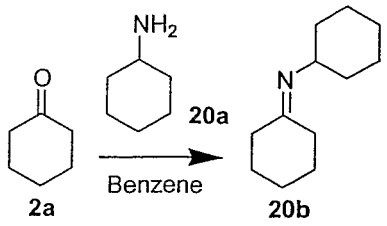
Compound **132** (prepared according to the procedure of Example 1, replacing Compound **1h** with 1-adamantan-1-yl-ethylamine) (25.0 mg, 0.052 mMol), $LiBH_4$ (lithium borohydride) (2.0 mg, 0.092 mMol) and methanol (0.01 mL) in ether (3.0 mL) were refluxed for 0.5 hr. The reaction was quenched with 1N HCl (2.0 mL). The organic layer was concentrated, extracted with DCM (dichloromethane) (2 x 5.0 mL) and dried over Na_2SO_4. The solvent was evaporated to give Compound **143** (22.0 mg, 96%) as a white solid.

MS *m/z* 440 (MH^+), 462 (MNa^+); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.71 (1H, d, J = 10.1 Hz), 3.82 (2H, m), 3.62 (1H, m), 3.41 (1H, m), 2.99 (1H, dd, J = 16.4, 5.0 Hz), 2.65 (1H, m), 2.47 (1H, m), 2.24 (1H, m), 2.03 (1H, m), 1.83 (10H, m), 1.52 (14H, m), 1.25 (4H, m), 1.03 (3H, d, J = 6.8 Hz).

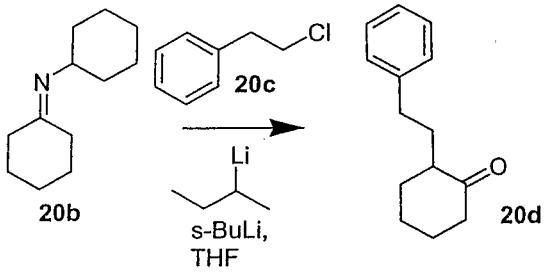
Example 20

2-[1-(4-fluoro-phenyl)-7-phenethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl]-ethenesulfonic acid (1-phenyl-ethyl)-amide (Cpd **258**)

2-[1-(4-fluoro-phenyl)-7-phenethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl]-ethenesulfonic acid (1-cyclohexyl-ethyl)-amide (Cpd **259**)

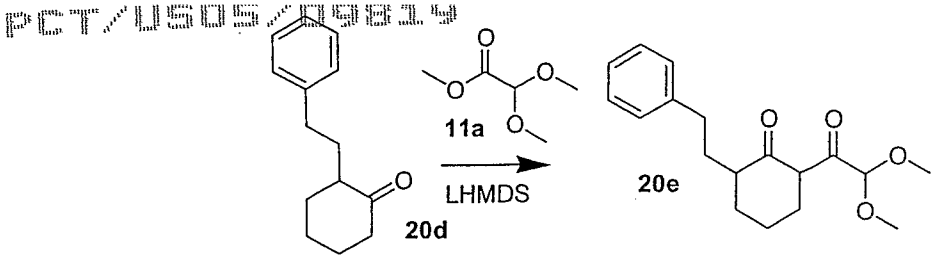


Cyclohexylamine Compound **20a** (4.64 g, 46.50 mmol) was added to a solution of cyclohexanone Compound **2a** (4.0 g, 46.50 mmol) in benzene (100 mL) at ambient temperature under a N_2 atmosphere. The mixture was refluxed at 80 °C for 5 hours, using a Dean Stark apparatus for the removal of water, and concentrated to dryness. The crude product was purified by distillation at aspirator pressure to afford cyclohexyl-cyclohexylidene-amine Compound **20b** (7.33 g, 88%) as a clear oil.

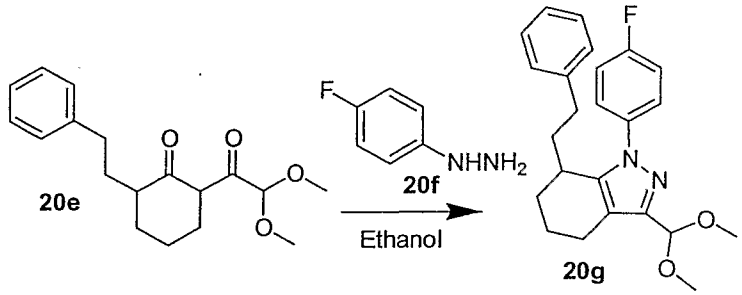


s-BuLi (28.0 mL, 1.3 M) was added slowly to a solution of Compound **20b** (7.0 g) in THF (50 mL) at -78 °C. The mixture stirred for 1 hr at -78 °C and then (2-chloro-ethyl)-benzene Compound **20c** (5.11 g, 36.4 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for 24 hrs while warming to r.t. The reaction was quenched with 1N HCl (5 mL), then diluted with water (100 mL) and EtOAc (500 mL). The organic layer was washed with brine, separated and dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude product. Purification by flash chromatography (eluted with 10% EtOAc in Hexane) afforded 2-phenethyl-cyclohexanone Compound **20d** (4.05 g, 20.0 mMol, 58%) as a yellow oil.

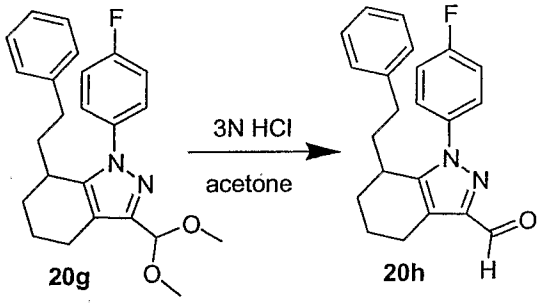
PCT/US05/09819



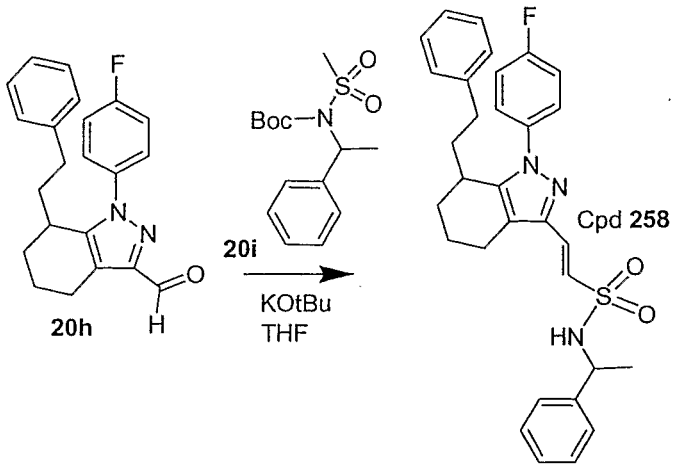
Compound **20d** was carried forward in place of Compound **2a** using the procedure of Example 11 to provide 2-(2,2-dimethoxy-acetyl)-6-phenethyl-cyclohexanone Compound **20e**.



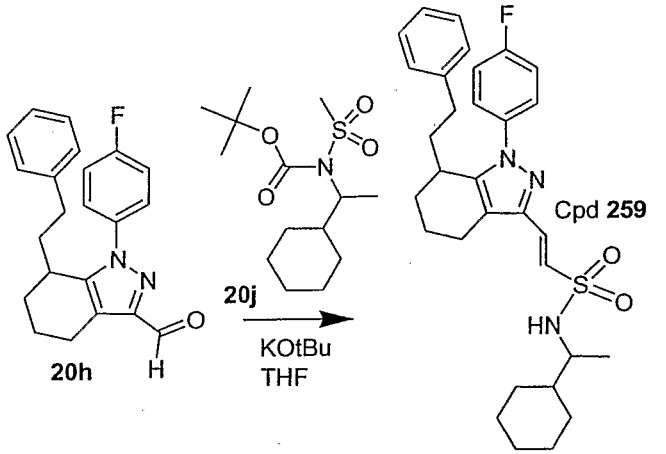
Using the procedure of Example 10, Compound **20e** was used in place of [3-(4-fluoro-benzylidene)-2-oxo-cyclohexyl]-oxo-acetic acid ethyl ester Compound **10c** and (4-fluoro-phenyl)-hydrazine Compound **20f** was used in place of (2,4-dichloro-phenyl)-hydrazine Compound **10d** to provide 1-[1-(4-fluoro-phenyl)-7-phenethyl-4,5,6,7-tetrahydro-1H-indazol-3-yl]-2,2-dimethoxy-ethanone Compound **20g**.



Using the procedure of Example 11, Compound **20g** was used in place of [3-(4-fluoro-benzylidene)-2-oxo-cyclohexyl]-oxo-acetic acid ethyl ester Compound **11d** to provide 1-(4-fluoro-phenyl)-7-phenethyl-4,5,6,7-tetrahydro-1H-indazole-3-carbaldehyde Compound **20h**.



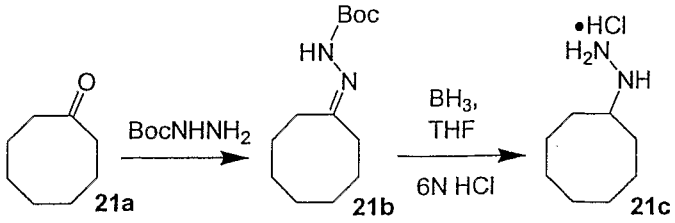
Using the procedure of Example 11, Compound **20h** was used in place of 1-benzyl-4,5,6,7-tetrahydro-1H-indazole-3-carbaldehyde Compound **11e** and (methylsulfonyl)(1-phenyl-ethyl)-carbamic acid tert-butyl ester Compound **20i** was used in place of (methylsulfonyl)[(1*R*)-1-phenyl-ethyl]-carbamic acid tert-butyl ester Compound **11f** to provide Compound **258**.



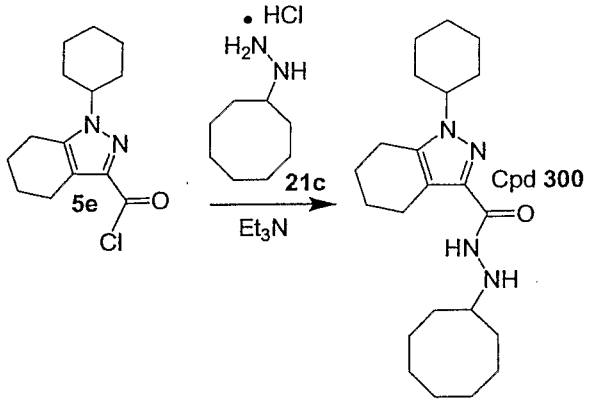
Using the procedure of Example 11, Compound **20h** was used in place of 1-benzyl-4,5,6,7-tetrahydro-1H-indazole-3-carbaldehyde Compound **11e** and (methylsulfonyl)(1-cyclohexyl-ethyl)-carbamic acid tert-butyl ester Compound **20j** was used in place of (methylsulfonyl)[(1*R*)-1-phenyl-ethyl]-carbamic acid tert-butyl ester Compound **11f** to provide Compound **259**.

Example 21

1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid N'-cyclooctyl-hydrazide (Cpd **300**)



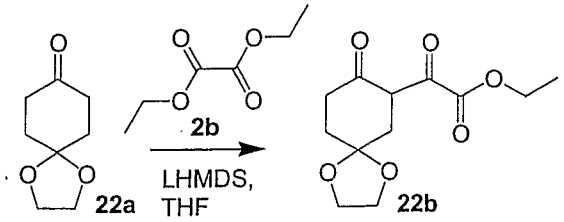
According to a published procedure, cyclooctanone Compound **21a** was reacted with hydrazinecarboxylic acid tert-butyl ester to produce an intermediate N'-cyclooctylidene-hydrazinecarboxylic acid tert-butyl ester Compound **21b** (as described in Ghali NK and Venton DL, *J. Org. Chem.*, **1981**, 46, 5413). According to the published procedure, Compound **21b** was carried forward to provide cyclooctyl-hydrazine hydrochloride Compound **21c**.



According to the procedure of Example 5, the acid chloride Compound **5e** was reacted with Compound **21c** in a solution of CH_2Cl_2 and triethylamine to provide an amide Compound **300**. MS *m/z* 345.1 (MH^+).

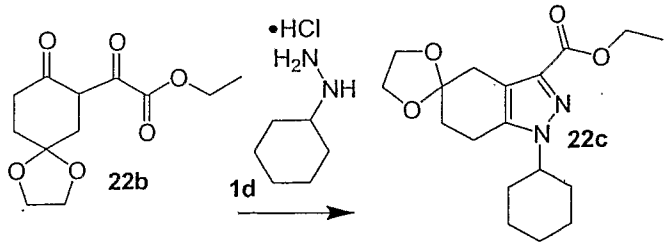
Example 22

1-cyclohexyl-5-oxo-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid (1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide (Cpd **96**)

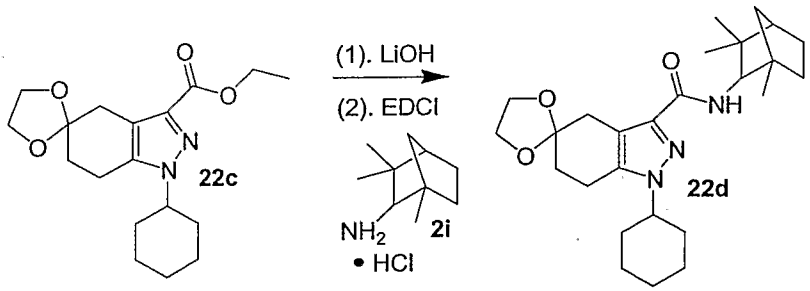


According to the procedure of Example 2, a solution of 1,4-

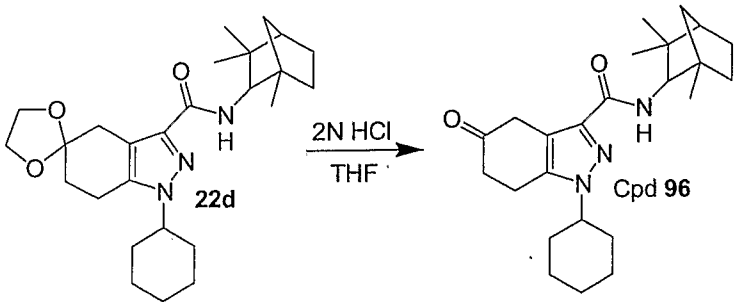
dioxaspiro[4.5]decane-8-one Compound **22a** in ether was added to a solution of LHMDS in ether at -78 °C. The diethyloxalate Compound **2b** was added to the mixture and reacted to produce an oxo-(8-oxo-1,4-dioxa-spiro[4.5]dec-7-yl)-acetic acid ethyl ester Compound **22b**.



According to the procedure of Example 1, Compound **22b** was reacted with a solution of cyclohexyl hydrazine hydrochloride Compound **1d** and K_2CO_3 in CH_2Cl_2 to produce (*N*-8-cyclohexyl-1,4-dioxa-spiro[4.6]-4,5,6,7-tetrahydro-1*H*-indazol-10-yl) carboxylic acid ethyl ester Compound **22c**.



According to the procedure of Example 8, Compound **22c** was used in place of 5-tert-butoxycarbonylamino-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid ethyl ester Compound **8c** and carried forward to provide (*N*-8-cyclohexyl-1,4-dioxa-spiro[4.6]-4,5,6,7-tetrahydro-1*H*-indazol-10-yl) carboxylic acid (1,3,3-trimethyl-bicyclo[2.2.1]hept-2-yl)-amide Compound **22d**.



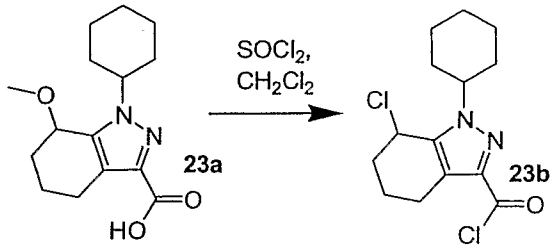
2N HCl (5 equiv.) was added to a solution of Compound **22d** (0.030 g 0.068 mMol) in THF (10 mL) at 0 °C. The mixture was stirred for 1 hr while warming to

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ambient temperature. The reaction was quenched with water (2 mL), neutralized to pH 7 with K_2CO_3 and diluted with EtOAc (20 mL). The organic layer was washed with water and brine, then separated, dried with anhydrous sodium sulfate and filtered. The product was concentrated *in vacuo* to afford Compound **96** (0.021 g, 79%) as a colorless oil. MS *m/z* 398 (MH^+).

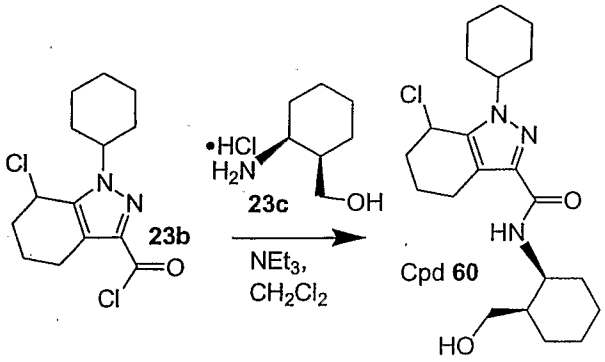
Example 23

7-chloro-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid [(1*S*,2*R*)-2-hydroxymethyl-cyclohexyl]-amide (Cpd **60**)



1-cyclohexyl-7-methoxy-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid Compound **23a** was prepared according to the procedure of Example 2, wherein 2-methoxy-cyclohexanone was used in place of Compound **2a** as the starting material.

Thionyl chloride (0.20 g, 1.7 mmol) was added to a solution of Compound **23a** (0.15 g, 0.55 mmol) in CH_2Cl_2 (10 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred for 3 hrs at 35 °C, cooled to ambient temperature, then concentrated *in vacuo* to afford the corresponding 7-chloro-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carbonyl chloride Compound **23b**.



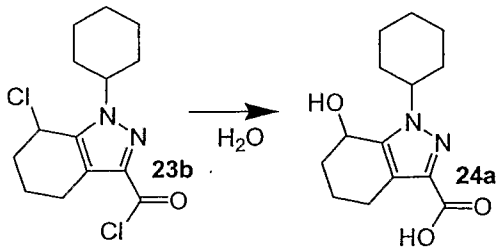
NEt_3 (triethylamine) (0.10 g, 0.98 mMol) and Compound **23b** (0.06, 0.20 mMol) were added to a solution of (1*R*,2*S*)-(2-amino-cyclohexyl)-methanol hydrochloride Compound **23c** (0.064 g, 0.39 mMol) in CH_2Cl_2 (10 mL) at ambient temperature under a N_2 atmosphere. The mixture was stirred at r.t. for 3 hrs, then

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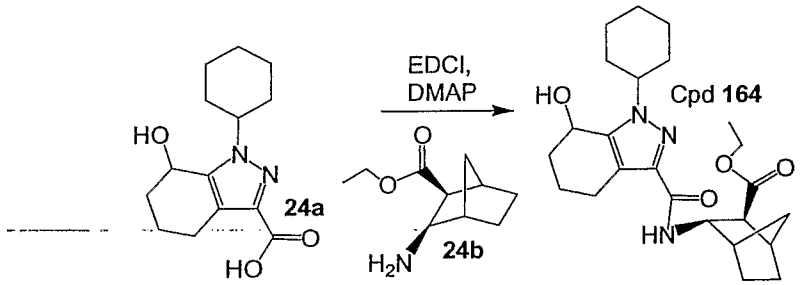
diluted with water (10 mL) and CH_2Cl_2 (50 mL). The organic layer was separated, dried with anhydrous sodium sulfate, then filtered and concentrated *in vacuo* to yield a crude product. Purification by flash chromatography (eluted with 20% EtOAc in hexane) afforded Compound **60** (0.034 g, 45%) as a white solid. MS *m/z* 394 (MH^+).

Example 24

(2*S*,3*R*)-3-[(1-cyclohexyl-7-hydroxy-4,5,6,7-tetrahydro-1H-indazole-3-carbonyl)-amino]-bicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester (Cpd **164**)



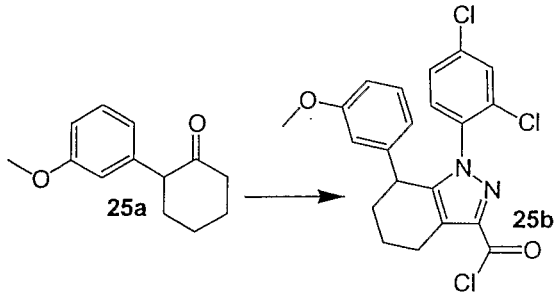
7-chloro-1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazole-3-carbonyl chloride Compound **23b** was hydrolyzed to provide 1-cyclohexyl-7-hydroxy-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid Compound **24a**.



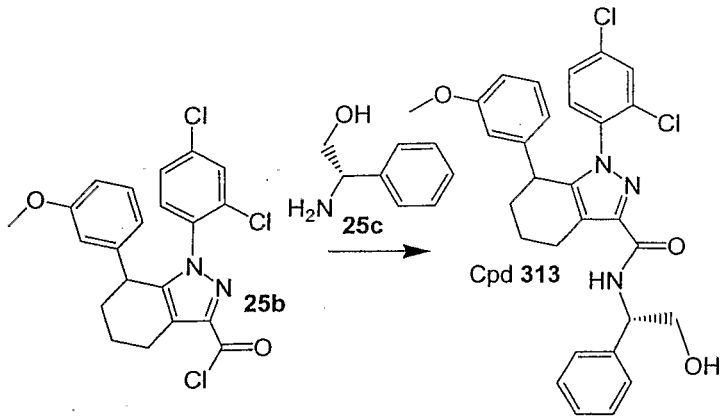
1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.15 g, 0.81 mmol), dimethylaminopyridine (DMAP) (8 mg) and (2*S*,3*R*)-3-amino-bicyclo[2.2.1]heptane-2-carboxylic acid ethyl ester Compound **24b** (0.059 g, 0.27 mmol) were added to a solution of 1-cyclohexyl-7-hydroxy-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid Compound **24a** (0.071 g, 0.27 mmol) in 5 mL CH_2Cl_2 at 0 °C under a N_2 atmosphere. The mixture was stirred for 6 hrs while warming to r.t., then concentrated *in vacuo* and purified by flash chromatography (eluted with 15% EtOAc in hexane) to afford Compound **164** (0.075 g, 65%) as a white solid.

Example 25

1-(2,4-dichloro-phenyl)-7-(3-methoxy-phenyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid [(1*S*)-2-hydroxy-1-phenyl-ethyl]-amide (Cpd **313**)



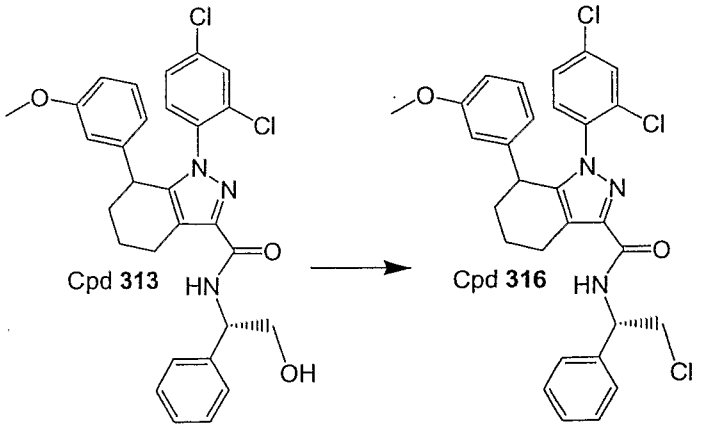
According to the procedure of Example 2, a solution of 2-(3-methoxy-phenyl)-cyclohexanone Compound **25a** (commercially available) in ether was carried forward in place of Compound **2a** to produce 1-(2,4-dichloro-phenyl)-7-(3-methoxy-phenyl)-4,5,6,7-tetrahydro-1H-indazole-3-carbonyl chloride Compound **25b**.



According to the procedure of Example 2, triethylamine and Compound **25b** were reacted with (1*S*)-2-amino-2-phenyl-ethanol Compound **25c** in CH_2Cl_2 to provide amide Compound **313**.

Example 26

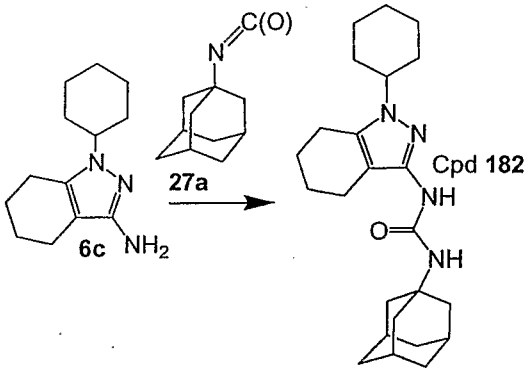
1-(2,4-dichloro-phenyl)-7-(3-methoxy-phenyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylic acid [(1*S*)-2-chloro-1-phenyl-ethyl]-amide (Cpd **316**)



Thionyl chloride (0.01 g, 0.08 mmol) was added to a solution of Compound **313** (0.02 g, 0.04 mmol) in 5 mL CH_2Cl_2 at 0 °C under a N_2 atmosphere. The mixture was stirred for 2 hrs while warming to ambient temperature, then concentrated *in vacuo* to afford the corresponding acid chloride. Purification by flash chromatography (eluted with 20% EtOAc in hexane) afforded Compound **316** (0.036 g, 95%) as a white solid. MS *m/z* 554 (MH^+).

Example 27

1-adamantan-1-yl-3-(1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-yl)-urea (Cpd **182**)



1-isocyanato-adamantane Compound **27a** (4.6 mg, 0.026 mMol) and triethyl amine (0.01 mL, 0.072 mMol) were added to a solution of 1-cyclohexyl-4,5,6,7-tetrahydro-1H-indazol-3-ylamine Compound **6c** (5 mg, 0.023 mMol) (Prepared using the procedure of Example 6). The mixture was stirred at r.t. for 4 hrs. The mixture was then concentrated and purified on a silica gel column (eluted with 15% EtOAc/hexane)

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to give Compound **182** (5.5 mg, 60%). MS *m/z* 397 (MH^+).

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

Biological Examples

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

Example 1

Binding Assay for CB1 or CB2 Agonists or Inverse Agonists

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

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

CB1 and CB2 Receptor Binding Results

The IC_{50} binding values for compounds tested were calculated by linear regression and were obtained from studies in which varying compound concentrations were used.

Table 1a

Cannabinoid CB1 Receptor Binding IC_{50} (μM)

Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
1	0.3767	**5**	6.8	**6**	6.75	**7**	3.1
9	0.3383	**10**	0.045	**11**	0.2854	**12**	0.1485
13	0.1084	**14**	0.216	**15**	0.2413	**16**	0.1851
17	0.1682	**18**	0.0918	**19**	0.114	**20**	0.169
21	0.044	**22**	1.03	**23**	1.8	**24**	3.81
25	0.0753	**26**	0.7233	**27**	0.108	**28**	0.85
29	0.7897	**30**	7.885	**31**	1.694	**32**	0.02
33	0.058	**34**	0.1356	**35**	0.7	**36**	0.1053
37	0.0693	**38**	0.006	**39**	0.009	**40**	1.44
41	0.049	**42**	10.7	**43**	0.014	**44**	0.079
45	0.04	**47**	22.6	**48**	0.249	**49**	0.15
50	0.255	**51**	15.2	**52**	6.26	**53**	6.12
54	11.4	**57**	10.897	**58**	0.736	**59**	0.34
60	5.235	**61**	2.195	**62**	0.28	**63**	13.655
64	0.41	**66**	3.59	**67**	0.3	**68**	0.4633
69	0.22	**70**	0.125	**71**	0.53	**72**	8.4
73	0.76	**74**	0.015	**75**	0.0237	**76**	1.96
77	0.052	**78**	4.6	**79**	0.03	**80**	0.23
81	0.49	**82**	0.7	**83**	0.038	**84**	0.4
85	0.6	**87**	0.855	**88**	2.4	**89**	3.7
90	1.84	**92**	1.6	**93**	1.15	**94**	1.78
95	6.4	**96**	9.5	**97**	9.7	**98**	20.5
99	0.96	**102**	30.9	**103**	2	**104**	17.1
105	8.5	**106**	12.7	**107**	0.91	**108**	2.4
119	0.006	**120**	2.46	**122**	0.004	**123**	0.0075
124	0.007	**125**	0.026	**126**	0.597	**127**	0.0099
128	0.01	**129**	0.0057	**130**	0.4	**131**	0.03
132	2.9	**133**	12	**134**	0.4	**135**	0.67
136	0.0008	**137**	3.95	**139**	0.16	**140**	0.89
141	0.3	**142**	0.6	**143**	2.4	**144**	0.22
145	0.95	**147**	2.075	**148**	0.013	**149**	0.067
150	0.13	**151**	0.59	**152**	0.34	**153**	1.39
154	0.06	**156**	0.097	**157**	0.03	**158**	0.013
159	0.74	**161**	5.235	**162**	0.635	**163**	4.77
164	6.01	**167**	1.66	**169**	0.43	**171**	0.64
173	0.444	**175**	2.16	**177**	10.45	**179**	7.3

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Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
180	0.7	**181**	0.3	**183**	0.05	**184**	0.05
185	0.9	**187**	3.69	**189**	0.01	**190**	1.62
192	0.06	**193**	0.12	**194**	0.0001	**195**	0.1
196	0.125	**197**	0.98	**198**	0.1	**199**	0.019
200	0.008	**201**	0.0017	**202**	0.1147	**203**	0.59
204	0.8	**205**	1.58	**206**	0.097	**207**	0.0824
208	0.66	**209**	0.26	**210**	0.335	**211**	0.005
212	0.26	**213**	0.95	**214**	1.23	**216**	2.8
217	0.0026	**218**	0.4	**219**	0.1	**221**	3.29
222	0.28	**223**	169.9	**224**	1.5	**226**	0.0079
227	2.77	**230**	0.01	**231**	0.6375	**232**	2.4
233	1.6	**234**	0.23	**235**	3.6	**236**	25.35
237	0.89	**238**	25.1	**241**	3.4	**242**	0.3
243	0.13	**244**	0.3	**245**	0.02	**246**	2.27
247	0.26	**248**	0.16	**249**	0.05	**250**	0.07
252	0.04	**253**	0.025	**256**	0.26	**265**	0.096
267	0.15	**269**	0.191	**270**	3.1	**271**	6.2
272	0.086	**273**	1.59	**274**	0.0187	**275**	0.323
276	0.135	**277**	1.3	**278**	0.4025	**279**	3.8
280	3.6	**281**	19.66	**282**	11.805	**283**	0.1
284	0.35	**285**	2.9	**287**	2.5	**289**	0.88
290	0.025	**291**	0.18	**292**	0.033	**293**	0.006
294	0.11	**295**	0.003	**296**	0.005	**297**	0.013
298	0.064	**301**	0.024	**304**	0.16	**305**	9.8
308	0.019	**309**	0.047	**320**	0.014	**321**	0.23
328	5.1	**329**	1.7	**330**	1.9	**331**	3
332	3.9	**333**	5.7	**334**	12.5	**336**	45
338	1.35	**339**	0.008	**340**	0.016	**341**	0.02
342	0.041	**343**	0.037	**344**	0.053	**345**	0.07
346	0.033	**347**	0.018	**348**	0.011	**349**	0.04
350	0.017	**351**	0.012	**353**	0.016	**356**	0.077
357	0.021	**358**	0.013	**360**	0.012	**362**	0.038
363	0.013	**364**	0.016	**365**	0.016	**368**	0.039
369	0.042	**371**	0.039	**373**	0.02	**374**	0.019
376	0.016	**377**	0.043	**380**	0.032	**381**	0.015
382	0.005	**383**	0.01	**384**	0.021	**385**	0.007
386	0.011	**387**	0.033	**388**	0.015	**389**	0.014
390	0.02	**393**	0.043	**394**	0.077	**395**	0.071
396	0.052	**397**	0.059	**398**	0.048		

Table 1b

Cannabinoid CB2 Receptor Binding IC_{50} (μM)

Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
1	0.0135	2	1.57	3	0.4285	4	3.69
5	0.2915	6	0.3665	7	3.575	8	21.22
9	0.0119	10	0.006	11	0.0406	12	0.0214
13	0.0065	14	0.0309	15	0.0538	16	0.0054
17	0.0045	18	0.0036	19	0.013	20	0.0352
21	0.011	22	0.143	23	0.1	24	6.82
25	0.0016	26	0.015	27	0.003	28	0.0075
29	0.1146	30	1.465	31	0.195	32	0.0069
33	0.008	34	0.0409	35	0.094	36	0.0128
37	0.112	38	0.0033	39	0.006	40	0.2147
41	0.0348	42	0.64	43	0.001	44	0.0024
45	0.0056	46	9.2	47	4.885	48	0.0553
49	0.0728	50	0.013	51	8.4177	52	4.9
53	0.23	54	6.05	55	7.9	56	20
57	2.2	58	0.1705	59	0.07	60	0.515
61	0.19	62	0.005	63	3.295	64	0.03
66	1.4	67	0.0155	68	0.057	69	0.0027
70	0.016	71	0.5	72	4.1	73	0.295
74	0.0014	75	0.0007	77	0.003	78	1.21
79	0.01	80	0.17	81	0.02	82	0.2
83	0.02	85	0.082	86	0.275	87	0.0266
88	0.087	89	0.0014	90	1.12	92	0.09
93	0.02	94	0.02	97	0.03	99	0.25
104	0.2	107	1.4	111	0.17	113	0.77
114	0.53	115	0.18	116	0.99	117	0.37
118	0.4	119	0.01	120	0.875	121	6.27
122	0.0015	123	0.0046	124	0.016	125	0.0022
126	0.593	127	0.0039	129	0.0017	130	0.005
131	0.01	132	0.0255	133	1.34	134	0.3
135	0.02	136	0.0005	137	1.55	138	11.8
139	0.3	140	3.4	141	0.14	142	0.4
143	1.26	144	0.04	145	1.1	147	1.79
148	0.03	149	0.008	150	0.04	151	0.03
152	0.2	153	0.06	154	0.37	156	0.002
157	0.002	158	0.009	159	0.13	160	3.5
161	0.775	162	0.11	163	0.21	164	0.49
165	0.8	166	1.7	167	0.028	169	0.017
170	0.3	171	0.3	173	0.526	174	16
175	1.56	176	4	177	2.4	178	2.9
179	0.7	180	1.7	181	1.6	182	0.028

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Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}	Cpd	IC_{50}
183	0.0069	**184**	0.02	**185**	0.12	**186**	2.29
187	1.6	**188**	5.1	**189**	0.01	**190**	4.5
191	0.19	**192**	0.002	**193**	0.005	**194**	0.0002
195	0.02	**196**	0.12	**197**	0.8	**198**	0.0057
199	0.01	**200**	0.001	**201**	0.002	**202**	0.0045
203	0.24	**204**	0.01	**205**	0.07	**206**	0.0141
207	0.0016	**208**	0.014	**209**	0.2	**210**	0.008
211	0.0007	**212**	0.074	**213**	0.2	**214**	0.0153
215	0.2	**216**	0.07	**217**	0.0001	**218**	0.003
219	0.004	**220**	0.23	**221**	0.46	**222**	0.0049
223	2.9	**224**	1.2	**225**	0.65	**226**	0.0055
227	1.1535	**228**	0.25	**229**	1.3	**230**	0.001
232	0.03	**233**	0.88	**234**	0.01	**235**	1.4
236	0.94	**237**	0.1513	**238**	3.7225	**239**	0.3
240	1.7	**241**	0.5	**242**	1.6	**243**	0.004
244	0.079	**245**	0.002	**246**	0.09	**247**	0.047
248	0.02	**250**	0.0056	**251**	0.0028	**252**	0.048
253	0.3	**256**	0.3	**265**	0.041	**267**	0.27
269	0.0386	**270**	1.8	**271**	2.6	**272**	0.07
273	0.414	**274**	0.0016	**275**	1.3	**276**	0.25
277	3.3	**278**	0.0375	**279**	0.83	**280**	0.679
281	16.5	**282**	3.805	**283**	0.1	**284**	0.045
285	2.4	**286**	2.7	**287**	2.1	**289**	0.4
290	1	**291**	1.7	**292**	0.06	**293**	0.6
294	0.7	**299**	5.5167	**301**	0.033	**302**	9.41
304	0.02	**305**	7.2	**306**	1.8	**321**	0.6
328	1.6	**329**	0.02	**330**	0.03	**331**	0.098
332	1.9	**333**	2.9	**334**	0.98	**336**	2.7
337	0.08	**338**	0.027				

Example 2

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

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

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

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adenylate cyclase activity. The binding of an inverse agonist inhibits the constitutive activity of the receptors and results in an increase in adenylate cyclase activity.

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

ASSAY

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

CELL GROWTH

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

CB1 RECEPTOR MEDIATED CHANGE IN CRE β-GAL EXPRESSION (TABLE 2A & 2B)

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

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

CB1 Receptor Results

The EC_{50} values for compounds tested were calculated by linear regression and were obtained from studies in which varying compound concentrations were used.

Table 2a

CB1 Receptor Functional Inverse Agonist EC_{50} (μM)

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
2	1.51	**7**	3.876	**9**	2.755	**28**	2.03
43	0.2947	**67**	0.5242	**70**	1	**73**	1.742
91	3.371	**144**	0.1759	**146**	1.515	**147**	0.1525
151	0.8008	**165**	1.034	**167**	3.36	**169**	0.05
220	0.399	**253**	1.94	**256**	0.25	**258**	0.48
259	0.61	**290**	0.044	**291**	0.01	**292**	0.009
293	0.025	**294**	0.14	**295**	<0.03	**296**	0.013
297	0.005	**298**	0.004	**305**	0.63	**307**	0.1
309	0.081	**312**	0.036	**316**	0.046	**319**	0.05
320	0.001	**321**	0.133				

Table 2b

CB1 Receptor Functional Agonist EC_{50} (μM)

Cpd	EC_{50}	Cpd	EC_{50}
33	0.135	**226**	0.52
38	0.103	**338**	0.0060
222	0.1945		

CB2 RECEPTOR MEDIATED CHANGE IN CRE β-GAL EXPRESSION (TABLE 2C & 2D)

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

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

CB2 Receptor Binding Results

The EC_{50} values for compounds tested were calculated by linear regression and were obtained from studies in which varying compound concentrations were used.

Table 2c

CB2 Receptor Functional Inverse Agonist EC_{50} (μM)

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
3	0.19	**67**	0.023	**70**	0.0459
116	0.5	**149**	0.0079	**156**	0.035
157	0.0015	**208**	0.0086	**209**	0.074
211	0.016	**214**	0.12	**215**	0.22

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Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
218	0.006	**219**	0.32	**220**	0.22
222	0.033	**226**	0.065	**231**	0.035
232	0.36	**251**	0.023	**284**	0.36

Table 2d

CB2 Receptor Functional Agonist EC_{50} (μM)

Cpd	EC_{50}	Cpd	EC_{50}	Cpd	EC_{50}
1	0.015	**10**	0.0019	**13**	0.0041
18	0.0027	**26**	0.011	**28**	0.33
32	0.047	**35**	0.035	**36**	0.005
37	0.01	**40**	0.031	**44**	0.029
62	0.00057	**75**	0.0001	**87**	0.25
94	0.025	**122**	0.037	**123**	0.0075
154	0.009	**184**	0.1	**195**	0.0055
207	0.01	**212**	0.0037	**217**	0.000052
278	0.00078	**338**	0.00000082		

Example 3

Effect of Sub-Chronic Treatment on Food Consumption and Body Weight Gain in Sprague-Dawley Rats

The effect of daily administration of a compound of the present invention was tested in male Sprague-Dawley rats. Animals in each dose group (n=6/group) were orally administered a daily dose of either a test compound (at a 3, 10 or 30 mg/Kg dose) or vehicle (50% PEG-400 in distilled water) in a volume of 2 mL/Kg of body weight immediately prior to the beginning of the dark phase each day for a period of 7 days.

Food consumption was electronically monitored during the dark and light phase that followed dosing (24 hrs total). The effect on food intake was expressed as the percent change of total food consumed in the 24 hr period after dosing to total food consumed in the 24 hr period prior to dosing.

EFFECT ON TOTAL FOOD CONSUMPTION

Animals at all three test compound dose levels had a relatively dose-dependent decrease in total food consumed compared to animals dosed with vehicle at the end of the treatment period.

EFFECT ON BODY WEIGHT GAIN

Animals at all three test compound dose levels had a dose-dependent decrease in body weight gain compared to animals in the vehicle chow group over the treatment period.

Example 4

Effect of Acute Treatment on Food Consumption in Sprague-Dawley Rats

The effect of acute, single-dose administration of a compound of the present invention was tested in male Sprague-Dawley rats. Animals in each dose group (n=6/group) were orally administered a single dose of either a test compound (at a 3, 10 or 30 mg/Kg dose) or vehicle (50% PEG-400 in distilled water) in a volume of 2 mL/Kg of body weight immediately prior to the beginning of the dark phase.

Food consumption was electronically monitored during the dark and light phase prior to dosing and the dark and light phase that followed dosing (48 hrs total). The effect on food intake was expressed as the percent change of total food consumed in the 24 hr period after dosing to total food consumed in the 24 hr period prior to dosing.

EFFECT ON TOTAL FOOD CONSUMPTION

Animals administered a single dose of the test compound at all three dose levels had a dose-dependent decrease in total food consumed compared to animals administered a single vehicle dose (p value <0.05 for 30 mg/Kg dose level).

Example 5

Effect of Chronic Treatment on Body and Epididymal Fat Pad Weight in Sprague-Dawley Rats

The effect of daily administration of a compound of the present invention was tested in male Sprague-Dawley rats. Animals were fed chow (10% Kcal) containing either a test compound (test chow) or vehicle (vehicle chow) over a 28 day treatment period. The test chow was formulated based upon the estimated daily consumption needed to achieve a 1, 3, 10 or 30 mg/kg dose level.

EFFECT ON BODY WEIGHT GAIN

Animals in the test chow groups had a dose-dependent decrease in body weight gain compared to animals in the vehicle chow group over the treatment period.

EFFECT ON EPIDIDYMAL FAT PAD WEIGHT

Animals in the test chow groups had a relatively dose-dependent decrease in epididymal fat pad weight compared to animals in the vehicle chow group over the treatment period (p value <0.01 for 30 mg/Kg dose level).

Example 6

Effect of Acute Treatment on Food Consumption and Meal Count in Ob/Ob Mice

The effect of acute, single-dose administration of a compound of the present invention was tested in hyperphagic obese ob/ob mice. Animals in each dose group (n=8/group) were orally administered a single dose of either a test compound (at a 3, 10

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or 30 mg/Kg dose) or vehicle (50% PEG-400 in distilled water) in a volume of 2 mL/Kg of body weight immediately prior to the beginning of the dark phase.

Food consumption was electronically monitored during the dark and light phase prior to dosing and the dark and light phase that followed dosing (48 hrs total). The effect on food intake was expressed as the percent change of total food consumed in the 24 hr period after dosing to total food consumed in the 24 hr period prior to dosing.

EFFECT ON TOTAL FOOD CONSUMPTION

Animals administered a single dose of the test compound at all three dose levels had a relatively dose-dependent decrease in total food consumed compared to animals administered a single vehicle dose (one-way ANOVA p value <0.05) and a downward trend in total meal count.

Example 7

Effect of Chronic Treatment on Body Weight Gain, Adipose Distribution, Energy Expenditure and Locomotor Activity in Ob/Ob Mice

The effect of daily administration of a compound of the present invention was tested in ob/ob mice. The mice were fed chow containing either a test compound (test chow) or vehicle (vehicle chow) over a 26 day treatment period. The test chow was formulated based upon the estimated daily consumption needed to achieve a 3, 10 or 30 mg/kg dose level.

EFFECT ON BODY WEIGHT GAIN

Animals in the 10 or 30 mg/kg test chow groups had a dose-dependent decrease in body weight gain compared to animals in the vehicle chow group over the treatment period.

EFFECT ON ADIPOSE DISTRIBUTION

Adipose distribution was measured by quantitative computerized tomography for mice in the 30 mg/kg test chow group.

Animals in the test chow group had a lower total mass (as measured by abdominal cross-section), a lower adipose mass and reduced visceral adipose compartments compared to animals in the vehicle chow group over the treatment period (one-way ANOVA p value <0.05). Lean mass for test chow animals was relatively unaffected.

EFFECT ON ENERGY EXPENDITURE AND LOCOMOTOR ACTIVITY

Energy expenditure was measured by indirect calorimetry measurements during both light and dark phases for mice in the 30 mg/kg test chow group.

Animals in the test chow group had a decreased respiratory quotient (CO_2/O_2), suggesting a shift in the primary fuel source from carbohydrates to fatty acids, an increased energy metabolism (O_2) and slightly increased spontaneous motor activity (as determined by summation of movement along the X, Y and Z axes) compared to animals in the vehicle chow group over the treatment period (one-way ANOVA p value <0.05).

Example 8

Effect of Chronic Treatment on Body, Epididymal Fat Pad and Liver Weight, Adipose Distribution, Energy Expenditure and Locomotor Activity and Plasma Triglyceride and Cholesterol Levels in Mice with Diet-Induced Obesity

The effect of daily administration of a compound of the present invention was tested in mice with diet-induced obesity (DIO). Obesity was induced by feeding "high-fat" (60% Kcal) chow to non-leptin-deficient mice over a 4 month period. The mice with DIO thus produced were then fed "high-fat" chow containing either a test compound (test chow) or vehicle (vehicle chow) over a 28 day treatment period. The test chow was formulated based upon the estimated daily consumption needed to achieve a 1, 3, 10 or 30 mg/kg dose level.

EFFECT ON BODY WEIGHT GAIN

Animals in all four test chow groups had a dose-dependent decrease in body weight gain compared to animals in the vehicle chow group over the treatment period.

EFFECT ON EPIDIDYMAL FAT PAD WEIGHT

Animals in all four test chow groups had either maintained epididymal fat pad weight or lost weight compared to animals in the vehicle chow group over the treatment period (one-way ANOVA p value <0.05).

EFFECT ON LIVER WEIGHT AND FAT CONTENT

Animals in all four test chow groups either maintained relatively the same liver weight or lost weight compared to animals in the vehicle chow group over the treatment period (one-way ANOVA p value <0.05).

Animals in the 10 and 30 mg/kg test chow groups tested for liver fat content also had a decrease in fat content (as a percent of total liver area) compared to animals in the vehicle chow group over the treatment period (one-way ANOVA p value <0.05).

EFFECT ON ADIPOSE DISTRIBUTION

Adipose distribution was measured by quantitative computerized tomography for mice in the 30 mg/kg test chow group.

Animals in the test chow group had a lower total mass (as measured by abdominal cross-section), a lower adipose mass and reduced visceral adipose compartments compared to animals in the vehicle chow group over the treatment period (one-way ANOVA p value <0.05). Lean mass for test chow animals was relatively unaffected.

EFFECT ON ENERGY EXPENDITURE AND LOCOMOTOR ACTIVITY

Energy expenditure was measured by indirect calorimetry measurements during both light and dark phases for mice in the 30 mg/kg test chow group.

Animals in the test chow group had a decreased respiratory quotient (CO_2/O_2), suggesting a shift in the primary fuel source from carbohydrates to fatty acids, an increased energy metabolism (O_2) and relatively no increase in spontaneous motor activity (as determined by summation of movement along the X, Y and Z axes) compared to animals in the vehicle chow group over the treatment period (one-way ANOVA p value <0.05).

EFFECT ON PLASMA TRIGLYCERIDE AND CHOLESTEROL LEVELS

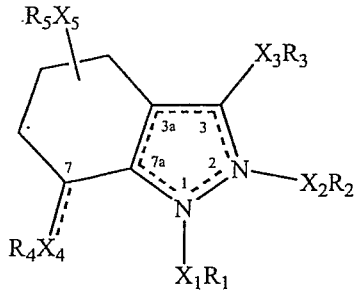
Animals in all four test chow groups had a decreased plasma triglyceride level compared to animals in the vehicle chow group over the treatment period (one-way ANOVA p value <0.05) and a downward trend in total cholesterol.

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

What is claimed is:

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

(I)



wherein

the dashed lines between positions 2-3 and positions 3a-7a in formula I represent locations for two double bonds present when X_1R_1 is present;

the dashed lines between positions 3-3a and positions 7a-1 in formula I represent locations for two double bonds present when X_2R_2 is present;

the dashed line between positions 7 and X_4R_4 in formula I represents the location for a double bond;

X_1 is absent, or is lower alkylene;

X_2 is absent, or is lower alkylene;

wherein only one of X_1R_1 and X_2R_2 are present;

X_3 is absent, or is lower alkylene, lower alkylidene or -NH-;

when the dashed line between positions 7 and X_4R_4 is absent, X_4 is absent, or is lower alkylene;

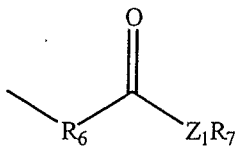
when the dashed line between positions 7 and X_4R_4 is present, X_4 is absent;

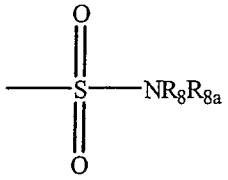
X_5 is absent, or is lower alkylene;

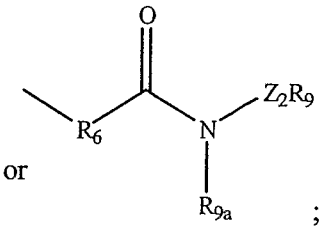
R_1 is selected from the group consisting of aryl, C_3-C_{12} cycloalkyl, or heterocyclyl, any of which are optionally substituted at one or more positions by halogen, lower alkyl, hydroxy or lower alkoxy;

R_2 is selected from the group consisting of aryl, C_3-C_{12} cycloalkyl, or heterocyclyl, any of which are optionally substituted at one or more positions by halogen, lower alkyl, hydroxy or lower alkoxy;

R_3 is



;


; or


;

when the dashed line between positions 7 and X_4R_4 is absent, R_4 is hydrogen; hydroxy; lower alkyl; lower alkoxy; halogen; aryl optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen; heterocyclyl optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen; or C_3-C_{12} cycloalkyl optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen;

when the dashed line between positions 7 and X_4R_4 is present, R_4 is CH-aryl wherein aryl is optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen; or CH-heterocyclyl wherein heterocyclyl is optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen;

R_5 is hydrogen; hydroxy; lower alkyl; lower alkoxy; hydroxy-lower alkylene-; carboxy; alkoxycarbonyl; aryloxycarbonyl; aryl-alkoxycarbonyl; NHR_{10}; $-C(O)NR_{11}R_{11a}$; $-O-C(O)-R_{12}$; oxo; or $-C(O)R_{13}$;

R_6 is absent, or is $-CH(R_{6a})-$;

R_{6a} is hydrogen; lower alkyl; or aryl optionally substituted by one or more of halogen, hydroxy, lower alkoxy, carboxy or alkoxycarbonyl;

R_7 is lower alkoxy; aryl optionally substituted by one or more hydroxy, halogen, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, hydroxy-alkylene-, $-NH(R_{6a})$, aryloxy, arylalkoxy, or aryl-lower alkylene; C_3-C_{12} cycloalkyl optionally substituted by one or more hydroxy, halogen, lower alkyl, lower

alkyl-aminocarbonyl, carboxy, alkoxycarbonyl, lower alkoxy, lower alkoxy-lower alkylene-, hydroxy-alkylene-, aryloxy, arylalkoxy, arylalkoxy-lower alkylene- optionally substituted on aryl by one or more hydroxy, halogen or lower alkyl; or aryl-lower alkylene; heterocyclyl optionally substituted by one or more hydroxy, halogen, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, lower alkoxy-lower alkylene-, hydroxy-alkylene-, aryloxy or arylalkoxy;

R_8, R_{8a}, R_9 and R_{9a} are each individually hydrogen; lower alkyl; $-NHR_{15}$; aryl optionally substituted by one or more hydroxy, halogen, $-NH(R_{6a})$, $-SO_2-NH(R_{6a})$, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, hydroxy-alkylene-, aryloxy or arylalkoxy; C_3-C_{12} cycloalkyl optionally substituted by one or more hydroxy, halogen, amino, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, hydroxy-alkylene-, aryloxy, arylalkoxy, or lower alkylene; or heterocyclyl optionally substituted by one or more hydroxy, halogen, amino, lower alkyl, carboxy, alkoxycarbonyl, lower alkoxy, hydroxy-alkylene-, aryloxy or arylalkoxy;

R_{10} is hydrogen, C_1-C_{10} alkoxycarbonyl optionally substituted at one or more positions by hydroxy, halogen or aryl; $-C(O)CF_3$; $-SO_2-NR_{14}R_{14a}$; -C(O)-heterocyclyl optionally substituted at one or more positions by hydroxy, halogen or aryl; $-C(O)NR_{14}R_{14a}$; $-SO_2$-aryl; $-SO_2R_{14}$; or $SO_2NR_{14}R_{14a}$;

R_{11}, R_{11a}, R_{12}, R_{13}, R_{14} and R_{14a} and R_{15} are each individually hydrogen; C_1-C_{10} alkyl; heterocyclyl; C_3-C_{12} cycloalkyl; or, aryl optionally substituted by lower alkyl, hydroxy, alkoxy, halogen $-SO_2-N(R_{6a})_2$, heterocyclyl or aryl-lower alkylene-;

Z_1 is absent; -NH-; or is lower alkylene optionally substituted at one or more positions by halogen, hydroxy, lower alkoxy, carboxy or lower alkoxycarbonyl;

Z_2 is absent; or is lower alkylene optionally substituted at one or more positions by aryl, cycloalkyl, halogen, hydroxy, lower alkyl, lower alkoxy, carboxy, alkoxycarbonyl or aryl;

or a pharmaceutically acceptable salt, isomer, prodrug, metabolite or polymorph thereof.

2. The compound of Claim 1 wherein X_1 is absent, or is lower alkylene, and R_1 is C_3-C_{12} cycloalkyl; or aryl optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen.

3. The compound of Claim 1 wherein the dashed line between positions 7 and X_4R_4 is absent; X_4 is absent, or is lower alkylene; and, R_4 is hydrogen; hydroxy; lower alkyl; lower alkoxy; halogen; aryl optionally substituted at one or more positions by lower alkoxy or halogen; heterocyclyl optionally substituted at one or more positions by halogen; or, C_3-C_8 cycloalkyl.

4. The compound of Claim 3 wherein the dashed line between positions 7 and X_4R_4 is absent; X_4 is absent; and, R_4 is hydrogen.

5. The compound of Claim 1 wherein R_3 is $-R_6C(O)NHZ_2R_9$.

6. The compound of Claim 5 wherein R_6 is absent; Z_2 is absent; or is lower alkylene optionally substituted by lower alkyl, lower alkoxy, carboxy, lower alkoxycarbonyl, hydroxy or halogen; and, R_9 is aryl optionally substituted by one or more hydroxy, halogen, $-NH(R_{6a})$, $-SO_2-NH(R_{6a})$, lower alkyl, lower alkoxy or arylalkoxy; C_5-C_{12} cycloalkyl optionally substituted at one or more positions by lower alkyl, lower alkoxy, hydroxy, amino, halogen or lower alkoxycarbonyl; or heterocyclyl.

7. The compound of Claim 1 wherein R_3 is $-R_6C(O)Z_1R_7$.

8. The compound of Claim 7 wherein R_6 is absent; and, R_7 is lower alkoxy; aryl optionally substituted by one or more hydroxy, lower alkoxy, $-NH(R_{6a})$ or arylalkoxy; C_3-C_{12} cycloalkyl optionally substituted by one or more lower alkyl, lower alkyl-aminocarbonyl, carboxy, alkoxycarbonyl, lower alkoxy-lower alkylene-, hydroxy-alkylene-, arylalkoxy-lower alkylene- optionally substituted on aryl by one or more halogen; or heterocyclyl optionally substituted by one or more lower alkyl, alkoxycarbonyl or lower alkoxy-lower alkylene-.

9. The compound of Claim 1 wherein X_3 is lower alkylidene; R_3 is $-SO_2NHR_8$; and, R_8 is aryl or C_5-C_{12} cycloalkyl.

10. The compound of Claim 1 wherein X_2 is absent, or is lower alkylene; and, R_2 is C_3-C_{12} cycloalkyl; or aryl optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen.

11. The compound of Claim 1 wherein the dashed line between positions 7 and X_4R_4 is present, X_4 is absent; and, R_4 is CH-aryl wherein aryl is optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen; or CH-heterocyclyl wherein heterocyclyl is optionally substituted at one or more positions by hydroxy, lower alkyl, lower alkoxy or halogen.

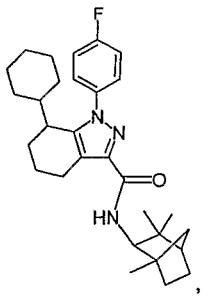
12. The compound of Claim 11 wherein aryl and heterocyclyl is each optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen.

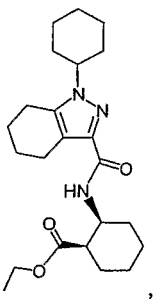
13. The compound of Claim 12 wherein aryl is phenyl and heterocyclyl is thienyl or furyl, wherein phenyl, thienyl or furyl is each optionally substituted at one or more positions by lower alkyl, lower alkoxy or halogen.

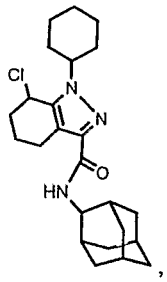
14. The compound of Claim 1 wherein X_5 is absent; and, R_5 is hydrogen; hydroxy; lower alkyl; hydroxy-lower alkylene-; carboxy; lower alkoxycarbonyl; aryl-alkoxycarbonyl; NHR_{10}; $-C(O)NR_{11}R_{11a}$; $-O-C(O)-R_{12}$; or oxo.

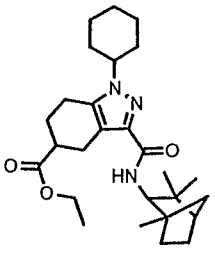
15. The compound of Claim 14 wherein R_{10} is hydrogen; C_1-C_{10} alkoxycarbonyl; $-C(O)CF_3$; -C(O)-heterocyclyl; $-C(O)NR_{14}R_{14a}$; or $-SO_2NR_{14}R_{14a}$; and wherein R_{11}, R_{11a}, R_{12}, R_{14} and R_{14a} are each individually hydrogen; C_1-C_{10} alkyl; or aryl optionally substituted by lower alkyl, heterocyclyl or aryl-lower alkylene-.

16. The compound of Claim 1 selected from the group consisting of:

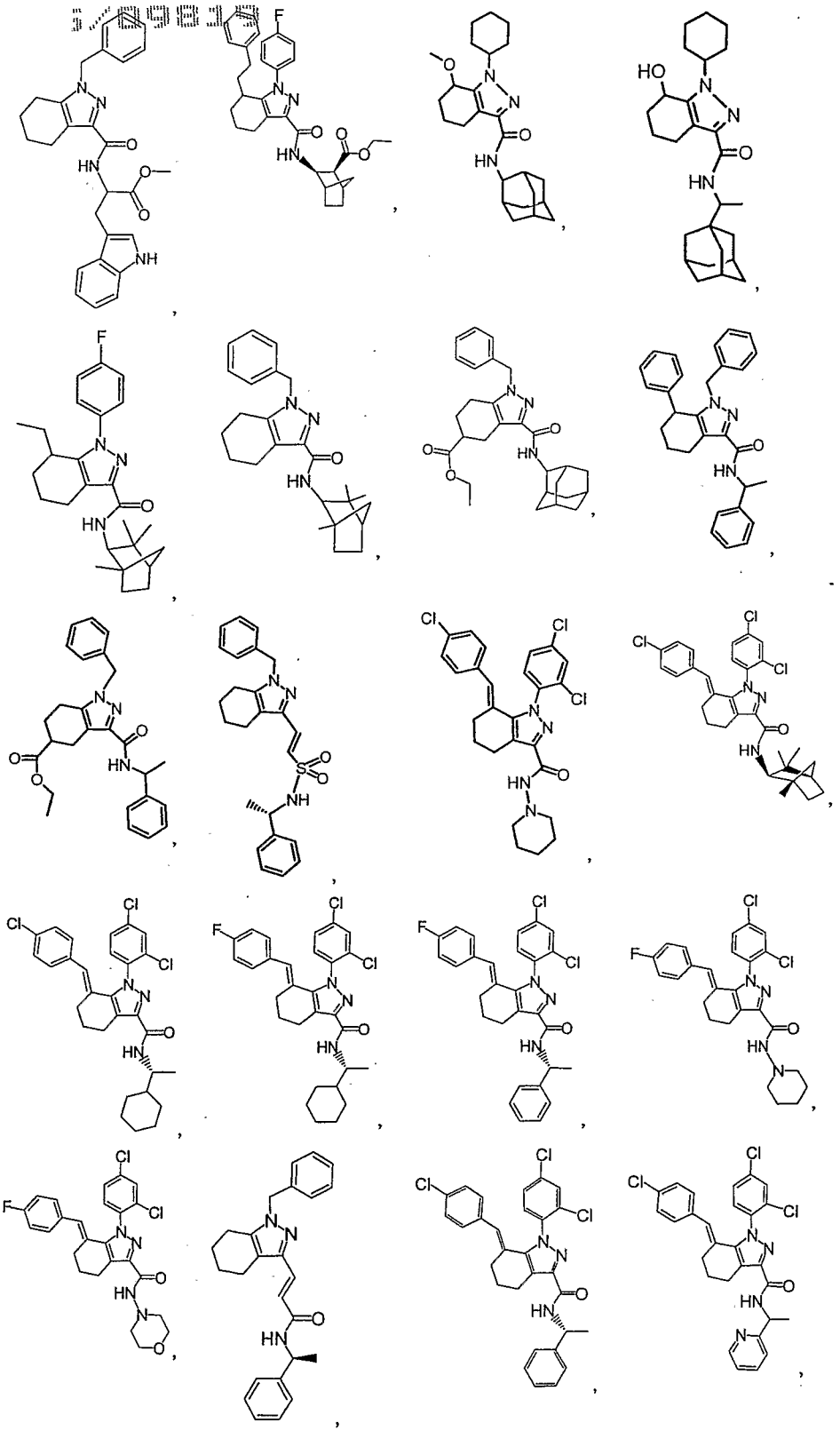


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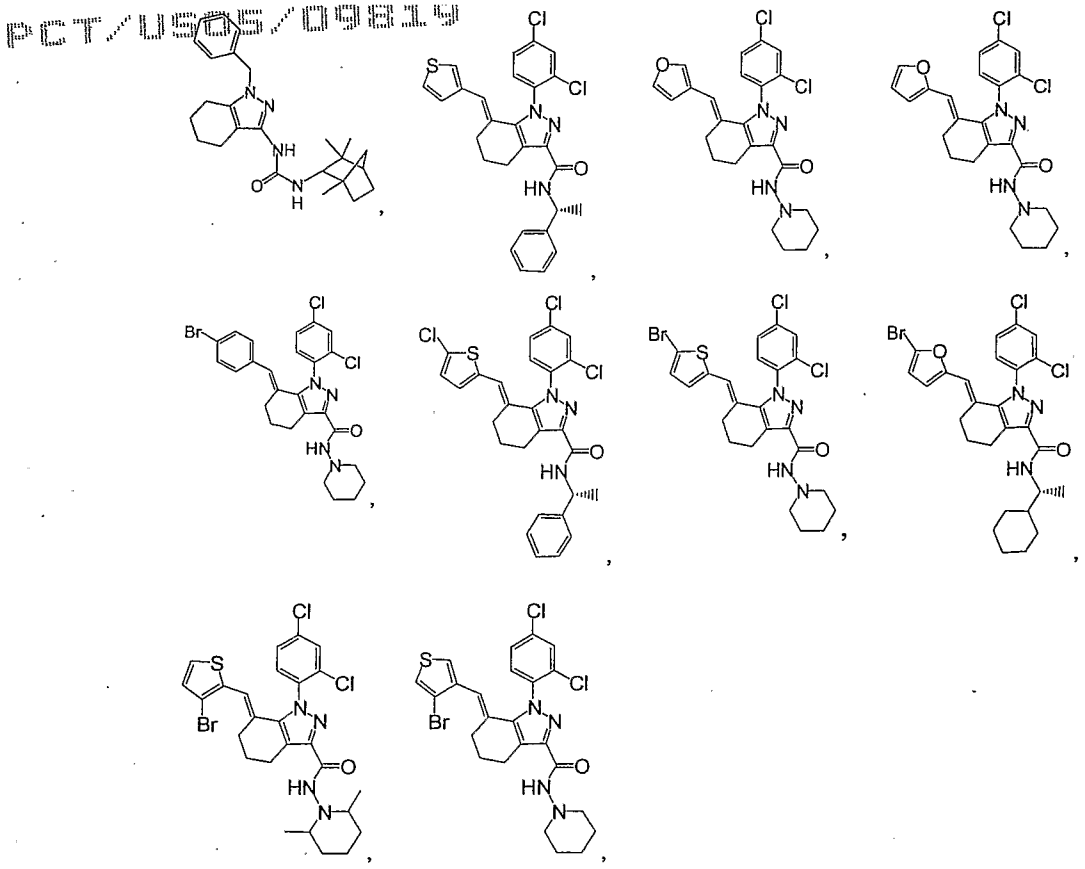
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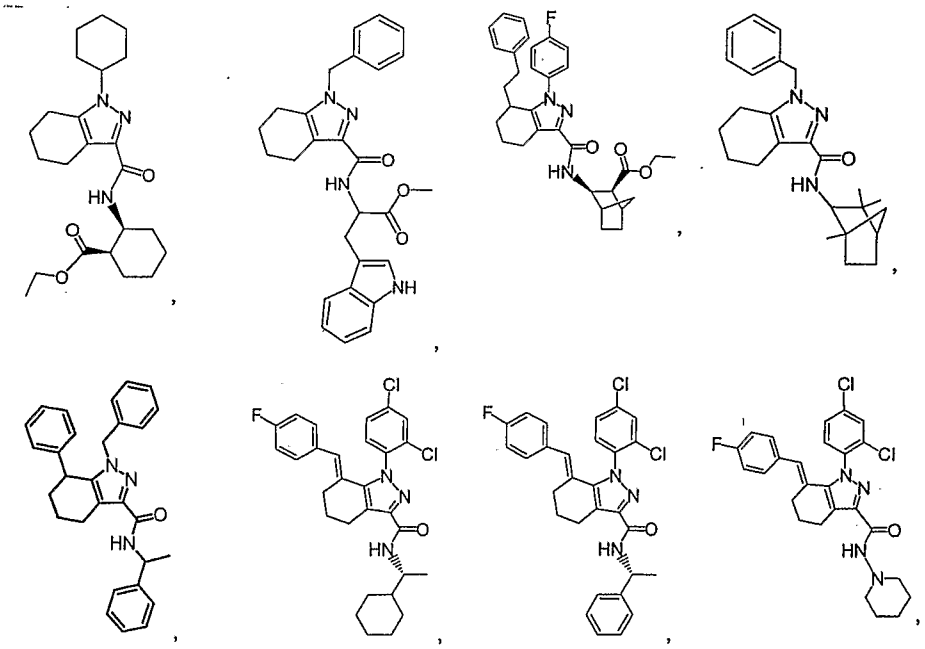


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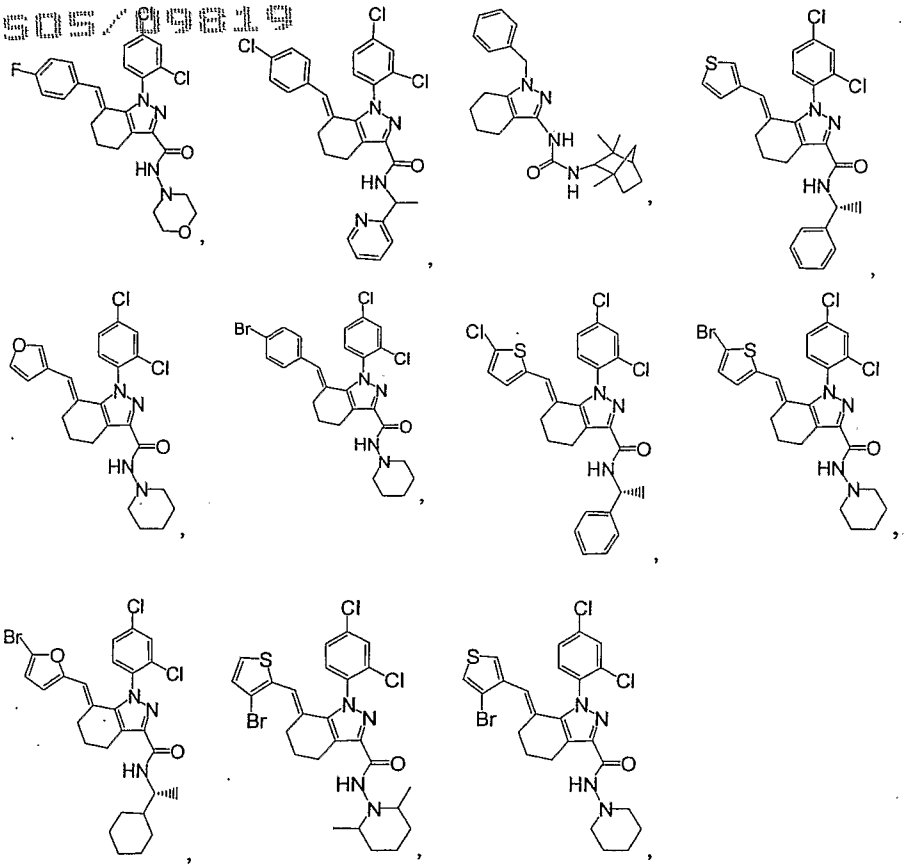


and pharmaceutically acceptable forms thereof.

17. The compound of Claim 16 selected from the group consisting of:



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and pharmaceutically acceptable forms thereof.

18. A method for treating, ameliorating or preventing a cannabinoid receptor mediated syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a compound of Claim 1.

19. The method of Claim 18 wherein the cannabinoid receptor is a CB1 or CB2 receptor; and, the compound of Claim 1 is an agonist, antagonist or inverse-agonist of the receptor.

20. The method of Claim 18 wherein the syndrome, disorder or disease is related to appetite, metabolism, diabetes, glaucoma-associated intraocular pressure, social and mood disorders, seizures, substance abuse, learning, cognition or memory, organ contraction or muscle spasm, respiratory disorders, locomotor activity or movement disorders, immune and inflammation disorders, unregulated cell growth, pain management or neuroprotection.

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4. The method of Claim 18 wherein the effective amount of the compound of Claim 1 is from about 0.001 mg/kg/day to about 300 mg/kg/day.

22. The method of Claim 18 further comprising treating, ameliorating or preventing a CB1 receptor inverse-agonist mediated appetite related, obesity related or metabolism related syndrome, disorder or disease in a subject in need thereof comprising the step of administering to the subject an effective amount of a CB1 inverse-agonist compound of Claim 1.

23. The method of Claim 22 wherein the effective amount of the compound of Claim 1 is from about 0.001 mg/kg/day to about 300 mg/kg/day.

24. The method of Claim 18 further comprising the step of administering to the subject a combination product and/or therapy comprising an effective amount of a compound of Claim 1 and a therapeutic agent.

25. The method of Claim 24 wherein the therapeutic agent is an anticonvulsant or a contraceptive agent.

26. The method of Claim 25 wherein the anticonvulsant is topiramate, analogs of topiramate, carbamazepine, valproic acid, lamotrigine, gabapentin, phenytoin and the like and mixtures or pharmaceutically acceptable salts thereof.

27. The method of Claim 25 wherein the contraceptive agent is a progestin-only contraceptive, a contraceptive having a progestin component and an estrogen component, or an oral contraceptive optionally having a folic acid component.

28. A method of contraception in a subject comprising the step of administering to the subject a composition, wherein the composition comprises a contraceptive and a CB1 receptor inverse-agonist or antagonist compound of Claim 1, wherein the composition reduces the urge to smoke in the subject and/or assists the subject in losing weight.