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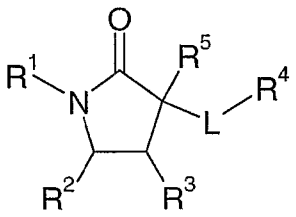
(54) Title: CANNABINOID RECEPTOR LIGANDS AND USES THEREOF



(I)

(57) Abstract: Compounds of Formula (I) that act as cannabinoid receptor ligands and their uses in the treatment of diseases linked to the mediation of the cannabinoid receptors in animals are described herein.

WO 2007/020502 A2

CANNABINOID RECEPTOR LIGANDS AND USES THEREOF

CROSS-REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/709,045 filed August 16, 2005 which is incorporated by reference herein in its entirety.

FIELD OF THE INVENTION

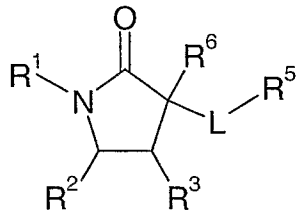
The present invention relates to pyrrolidone compounds as cannabinoid receptor ligands, in particular CB1 receptor antagonists, and uses thereof for treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists.

BACKGROUND

CB1 cannabinoid receptor antagonists/inverse agonists have been shown and/or suggested to be useful for a variety of diseases, conditions or disorders, including indications such as eating disorders (e.g., binge eating disorder, anorexia, and bulimia), weight loss or control (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), substance abuse, addictive disorders, impulsivity, alcoholism (e.g., alcohol abuse, addiction and/or dependence including treatment for abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including treatment for craving reduction and relapse prevention of tobacco smoking), dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), sexual dysfunction in males (e.g., erectile difficulty), seizure disorders, epilepsy, inflammation, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), attention deficit disorder (ADD/ADHD), Parkinson's disease, and type II diabetes. Although investigations are on-going, there still exists a need for a more effective and safe therapeutic treatment having less side effects.

SUMMARY

The present invention provides compounds of Formula (I) that act as cannabinoid receptor ligands (in particular, CB1 receptor antagonists)



(I)

wherein

R^1 and R^2 are each independently a chemical moiety selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, pyrazinyl, 3-6 membered partially or fully saturated heterocycle containing 1 to 3 heteroatoms each independently selected from oxygen, nitrogen or sulfur, and 3-7 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents (preferably, R^1 is phenyl, 2-pyridinyl or 3-pyridinyl, where said phenyl, said 2-pyridinyl and said 3-pyridinyl are optionally substituted with one to three substituents each independently selected from halo, cyano, hydroxyl, $(C_1$-$C_4)$alkyl, -C(O)-R^4, halo-subsituted $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkylamino or di$(C_1$-$C_4)$alkylamino; and

R^2 is phenyl optionally substituted with one to three substituents each independently selected from halo, cyano, hydroxyl, $(C_1$-$C_4)$alkyl, -C(O)-R^4, halo-subsituted $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkylamino or di$(C_1$-$C_4)$alkylamino);

R^3 is hydrogen, $(C_1$-$C_4)$alkyl, or a halo-substituted $(C_1$-$C_4)$alkyl;

L is a bond, -O-, -O-CH_2-, $(C_1$-$C_3)$alkyl, $(C_2$-$C_3)$alkenyl, $(C_2$-$C_3)$alkynyl, –CH(OH)-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)S-, -NR^4-, -NR^4-($(C_1$-$C_4)$alkyl)-, -C(O)NR^4-, or -CH_2-C(O)-NR^4-;

R^4 is hydrogen, or $(C_1$-$C_4)$alkyl (preferably, R^4 is hydrogen, methyl or ethyl);

R^5 is a chemical moiety selected from the group consisting of $(C_1$-$C_8)$alkyl, phenyl$(C_1$-$C_4)$alkyl, phenyl, 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen or sulfur, 3- to 6-membered partially or fully saturated heterocycle containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen or sulfur, partially or fully saturated $(C_3$-$C_7)$ cycloalkyl, and 5- to 6-membered lactone or lactam, where said moiety is optionally substituted with one or more substituents each independently selected from halo, hydroxy, cyano, nitro, $(C_1$-$C_4)$alkyl, partially or fully saturated $(C_3$-$C_7)$ cycloalkyl, halo-substituted$(C_1$-$C_4)$alkyl, hydroxy$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, halo-substituted$(C_1$-$C_4)$alkoxy, γ-butryolactam, γ-butryolactone, -C(O)-R^4, -OC(O)-R^4, -C(O)-O-R^4, -N(R^4)-C(O)-R^4, -C(O)-N(R^4)(R^4), -N(R^4)-C(O)-O-R^4, -O-C(O)-O-R^4, phenylsulfonyl, $(C_1$-$C_4)$alkylsulfonyl, benzyl, phenyl, pyridinyl, or pyrimidinyl, where said phenyl is optionally substituted with one to three substituents each independently selected from chloro, fluoro or methyl; and

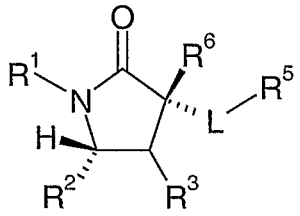
R^6 is hydrogen, $(C_1$-$C_7)$alkyl, phenyl, or phenyl$(C_1$-$C_4)$alkyl-, where said phenyl is optionally substituted with one to three substituents each independently selected from fluoro, $(C_1$-$C_4)$alkyl, or $(C_1$-$C_4)$alkoxy;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

In one preferred embodiment of the present invention, L is -NR^4-,or -NR^4-($(C_1$-$C_4)$alkyl)-; and R^6 is hydrogen, or $(C_1$-$C_7)$alkyl. R^5 is preferably $(C_4$-$C_8)$alkyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, pyridinyl, or phenyl, where said phenyl is optionally substituted with one or two substituents each independently selected from fluoro, chloro, cyano, nitro, $(C_1$-$C_4)$alkyl, fluoro-substituted$(C_1$-$C_4)$alkyl, hydroxyl$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, fluoro-substituted$(C_1$-

C_4)alkoxy, γ-butryolactam, -C(O)-OCH_3, or -C(O)-NH_2, where the piperidinyl and the piperazinyl are optionally substituted with phenylsulfonyl, (C_1-C_4)alkylsulfonyl, benzyl, phenyl, pyridinyl, or pyrimidinyl;

When L is -NR^4-,or -NR^4-((C_1-C_4)alkyl)-, the compound of Formula (I) preferably has the following stereochemistry (Formula (II) shown below)



(II)

where R^1, R^2, R^3, R^5, R^6, and L are as defined for the compound of Formula (I) above.

In another preferred embodiment of the present invention, L is (C_1-C_3)alkyl; and R^6 is hydrogen, (C_1-C_7)alkyl, or phenyl(C_1-C_4)alkyl-, where said phenyl is optionally substituted with one to three substituents each independently selected from fluoro, (C_1-C_4)alkyl, or (C_1-C_4)alkoxy; a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

When L is (C_1-C_3)alkyl, R^5 is preferably phenyl or a partially or fully saturated cyclohexyl, where said phenyl is optionally substituted with one or two substituents each independently selected from fluoro, chloro, cyano, nitro, (C_1-C_4)alkyl, halo-substituted(C_1-C_4)alkyl, (C_1-C_4)alkoxy, and phenyl.

In yet another preferred embodiment of the present invention, L is a bond; and R^6 is hydrogen, or (C_1-C_7)alkyl; a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

When L is a bond, R^5 is preferably a chemical moiety selected from the group consisting of 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen or sulfur, 5- to 6-membered fully saturated heterocycle containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen or sulfur, where said moiety is optionally substituted with one or more substituents each independently selected from hydroxy, (C_1-C_4)alkyl, partially or fully saturated (C_3-C_7) cycloalkyl, benzyl, phenyl, pyridinyl, or pyrimidinyl.

In yet another preferred embodiment of the present invention, L is –O or -O-CH_2-; and R^6 is hydrogen or (C_1-C_7)alkyl; a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

When L is –O or -O-CH_2-, R^5 is a chemical moiety selected from the group consisting of phenyl(C_1-C_4)alkyl and phenyl, where said moiety is optionally substituted with one to three substituents each independently selected from halo, cyano, nitro, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy, -C(O)-R^4, or phenyl.

Some of the compounds described herein contain at least one chiral center; consequently, those skilled in the art will appreciate that all stereoisomers (e.g., enantiomers and

diasteroisomers) of the compounds illustrated and discussed herein are within the scope of the present invention. In addition, tautomeric forms of the compounds are also within the scope of the present invention. Those skilled in the art will recognize that chemical moieties such as an alpha-amino ether or an alpha-chloro amine may be too unstable to isolate; therefore, such moieties do not form a part of this invention.

Compounds of the present invention have been shown to be useful cannabinoid receptor ligands (in particular, CB1 receptor antagonists). Accordingly, another aspect of the present invention is a pharmaceutical composition that comprises (1) a compound of the present invention, and (2) a pharmaceutically acceptable excipient, diluent, or carrier. Preferably, the composition comprises a therapeutically effective amount of a compound of the present invention. The composition may also contain at least one additional pharmaceutical agent (described herein). Preferred agents include nicotine receptor partial agonists, opioid antagonists (e.g., naltrexone and nalmefene), dopaminergic agents (e.g., apomorphine), attention deficit disorder (ADD including attention deficit hyperactivity disorder (ADHD)) agents (e.g., Ritalin™, Strattera™, Concerta™ and Adderall™), and anti-obesity agents (described herein below).

In yet another embodiment of the present invention, a method for treating a disease, condition or disorder modulated by a cannabinoid receptor (preferably, a CB1 receptor) antagonists in animals that includes the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention (or a pharmaceutical composition thereof). Diseases, conditions, and/or disorders modulated by cannabinoid receptor antagonists include a variety of indications described herein below. In a preferred embodiment, the method is used in promoting weight loss (including prevention of weight gain), or treatment of obesity or obesity related eating disorders, Parkinson's disease, dementia, alcoholism, tobacco abuse, or a deficiency in attention (e.g., ADD/ADHD) and/or cognition.

Compounds of the present invention may be administered in combination with other pharmaceutical agents. Preferred pharmaceutical agents include nicotine receptor partial agonists, opioid antagonists (e.g., naltrexone (including naltrexone depot), antabuse, and nalmefene), dopaminergic agents (e.g., apomorphine), ADD/ADHD agents (e.g., methylphenidate hydrochloride (e.g., Ritalin™ and Concerta™), atomoxetine (e.g., Strattera™), and amphetamines (e.g., Adderall™)) and anti-obesity agents, such as those described herein below.

The combination therapy may be administered as (a) a single pharmaceutical composition which comprises a compound of the present invention, at least one additional pharmaceutical agent described herein and a pharmaceutically acceptable excipient, diluent, or carrier; or (b) two separate pharmaceutical compositions comprising (i) a first composition comprising a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier, and (ii) a second composition comprising at least one additional

pharmaceutical agent described herein and a pharmaceutically acceptable excipient, diluent, or carrier. The pharmaceutical compositions may be administered simultaneously or sequentially and in any order.

Definitions

As used herein, the term "alkyl" refers to a hydrocarbon radical of the general formula C_nH_{2n+1}. The alkane radical may be straight or branched. For example, the term "(C_1-C_6)alkyl" refers to a monovalent, straight, or branched aliphatic group containing 1 to 6 carbon atoms (e.g., methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl, *t*-butyl, *n*-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, neopentyl, 3,3-dimethylpropyl, hexyl, 2-methylpentyl, and the like). Similarly, the alkyl portion (i.e., alkyl moiety) of an alkoxy, acyl (e.g., alkanoyl), alkylamino, dialkylamino, and alkylthio group have the same definition as above. When indicated as being "optionally substituted", unless specified otherwise, the alkane radical or alkyl moiety may be unsubstituted or substituted with one or more substituents (generally, one to three substituents except in the case of halogen substituents such as perchloro or perfluoroalkyls) independently selected from the group of substituents listed below in the definition for "substituted." "Halo-substituted alkyl" refers to an alkyl group substituted with one or more halogen atoms (e.g., fluoromethyl, difluoromethyl, trifluoromethyl, perfluoroethyl, and the like). When substituted, the alkane radicals or alkyl moieties are preferably substituted with 1 to 3 fluoro substituents, or 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_2-C_3)alkenyl, optionally substituted aryl, optionally substituted 5-6 membered heteroaryl, 3- to 6-membered partially or fully saturated heterocycle, chloro, cyano, hydroxy, (C_1-C_3)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_4)alkyl amino, aminocarboxylate (i.e., (C_1-C_6)alkyl-O-C(O)-NH-), hydroxy(C_2-C_3)alkylamino, or keto (oxy), and more preferably, 1 to 3 fluoro groups, or 1 substituent selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_6)aryl, 6-membered-heteroaryl, 3- to 6-membered heterocycle, (C_1-C_3)alkoxy, (C_1-C_4)alkyl amino or di-(C_1-C_2)alkyl amino.

The terms "partially or fully saturated carbocyclic ring" (also referred to as "partially or fully saturated cycloalkyl") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiral ring. Unless specified otherwise, the carbocyclic ring is generally a 3- to 8-membered ring. For example, partially or fully saturated carbocyclic rings (or cycloalkyl) include groups such as cyclopropyl, cyclopropenyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclpentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, norbornyl (bicyclo[2.2.1]heptyl), norbornenyl, bicyclo[2.2.2]octyl, and the like. When designated as being "optionally substituted", unless specified otherwise, the partially saturated or fully saturated cycloalkyl group may be unsubstituted or substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted." A substituted carbocyclic ring also includes groups wherein the carbocyclic ring is fused to a phenyl ring (e.g., indanyl). The carbocyclic group may be attached to the chemical entity or moiety by any one of the carbon atoms within the carbocyclic ring system. When substituted, the carbocyclic group is preferably

substituted with 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_1-C_6)alkylidenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, fluoro, cyano, hydroxy, (C_1-C_3)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_4)alkyl amino, aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), hydroxy(C_2-C_3)alkylamino, or keto (oxy), and more preferably 1 or 2 from substituents independently selected from (C_1-C_2)alkyl, 3- to 6-membered heterocycle, fluoro, (C_1-C_3)alkoxy, (C_1-C_4)alkyl amino or di-(C_1-C_2)alkyl amino. In addition, the substituent may be added across the carbocyclic ring to form a bicyclic structure. For example, -C(O)-O- bridged across a cyclopentane ring to form a lactone, such as 3-oxo-2-oxa-bicyclo[2.2.1]heptane. Similarly, any cycloalkyl portion of a group (e.g., cycloalkylalkyl, cycloalkylamino, etc.) has the same definition as above.

The term "partially saturated or fully saturated heterocyclic ring" (also referred to as "partially saturated or fully saturated heterocycle") refers to nonaromatic rings that are either partially or fully hydrogenated and may exist as a single ring, bicyclic ring or a spiral ring. Unless specified otherwise, the heterocyclic ring is generally a 3- to 6-membered ring containing 1 to 3 heteroatoms (preferably 1 or 2 heteroatoms) independently selected from sulfur, oxygen and/or nitrogen. Partially saturated or fully saturated heterocyclic rings include groups such as epoxy, aziridinyl, tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, pyrrolidinyl, N-methylpyrrolidinyl, imidazolidinyl, imidazolinyl, piperidinyl, piperazinyl, pyrazolidinyl, 2H-pyranyl, 4H-pyranyl, 2H-chromenyl, oxazinyl, morpholino, thiomorpholino, tetrahydrothienyl, tetrahydrothienyl 1,1-dioxide, and the like. When indicated as being "optionally substituted", unless specified otherwise, the partially saturated or fully saturated heterocycle group may be unsubstiuted or substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted." A substituted heterocyclic ring includes groups wherein the heterocyclic ring is fused to an aryl or heteroaryl ring (e.g., 2,3-dihydrobenzofuranyl, 2,3-dihydroindolyl, 2,3-dihydrobenzothiophenyl, 2,3-dihydrobenzothiazolyl, 3,4-dihydro-1*H*-isoquinolinyl, etc.). When substituted, the heterocycle group is preferably substituted with 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, (C_2-C_4)alkenyl, (C_1-C_6)alkyl-SO_2-, aryl, heteroaryl, 3- to 6-membered heterocycle, chloro, fluoro, cyano, hydroxy, (C_1-C_3)alkoxy, aryloxy, aryl-(C_1-C_4)alkyl, aryl-SO_2-, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), or keto (oxy), and more preferably with 1 or 2 substituents independently selected from (C_1-C_3)alkyl, (C_3-C_6)cycloalkyl, phenyl, 5- or 6-membered-heteroaryl, 3- to 6-membered heterocycle, or fluoro. The heterocyclic group may be attached to the chemical entity or moiety by any one of the ring atoms within the heterocyclic ring system. Similarly, any heterocycle portion of a group (e.g., heterocycle-substituted alkyl, heterocycle carbonyl, etc.) has the same definition as above.

The term "aryl" or "aromatic carbocyclic ring" refers to aromatic moieties having a single (e.g., phenyl) or a fused ring system (e.g., naphthalene, anthracene, phenanthrene, etc.). A typical aryl group is a 6- to 10-membered aromatic carbocyclic ring(s). A preferred aryl group is phenyl. When indicated as being "optionally substituted", unless specified otherwise, the aryl

groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) independently selected from the group of substituents listed below in the definition for "substituted." Substituted aryl groups include a chain of aromatic moieties (e.g., biphenyl, terphenyl, phenylnaphthalyl, etc.). When substituted, the aromatic moieties are preferably substituted with 1 to 3 substituents independently selected from (C_1-C_4)alkyl, (C_2-C_3)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, bromo, chloro, fluoro, iodo, cyano, nitro, hydroxy, (C_1-C_4)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, or aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), and more preferably, 1 or 2 substituents independently selected from (C_1-C_4)alkyl, chloro, fluoro, cyano, hydroxy, nitro, or (C_1-C_4)alkoxy. The aryl group may be attached to the chemical entity or moiety by any one of the carbon atoms within the aromatic ring system. Similarly, the aryl portion (i.e., aromatic moiety) of an aroyl, aroyloxy (i.e., (aryl)-C(O)-O-), aryl-alkyl, and the like, has the same definition as above.

The term "heteroaryl" or "heteroaromatic ring" refers to aromatic moieties containing at least one heteratom (e.g., oxygen, sulfur, nitrogen or combinations thereof) within a 5- to 10-membered aromatic ring system (e.g., pyrrolyl, pyridyl, pyrazolyl, indolyl, indazolyl, thienyl, furanyl, benzofuranyl, oxazolyl, imidazolyl, tetrazolyl, triazinyl, pyrimidyl, pyrazinyl, thiazolyl, purinyl, benzimidazolyl, quinolinyl, isoquinolinyl, benzothiophenyl, benzoxazolyl, etc.). The heteroaromatic moiety may consist of a single or fused ring system. A typical single heteroaryl ring is a 5- to 6-membered ring containing one to three heteroatoms independently selected from oxygen, sulfur and nitrogen and a typical fused heteroaryl ring system is a 9- to 10-membered ring system containing one to four heteroatoms independently selected from oxygen, sulfur and nitrogen. When indicated as being "optionally substituted", unless specified otherwise, the heteroaryl groups may be unsubstituted or substituted with one or more substituents (preferably no more than three substituents) independently selected from the group of substituents listed below in the definition for "substituted." When substituted, the heteroaromatic moieties are preferably substituted with 1 or 2 substituents independently selected from (C_1-C_4)alkyl, (C_2-C_3)alkenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, bromo, chloro, fluoro, iodo, cyano, hydroxy, (C_1-C_4)alkoxy, aryloxy, amino, (C_1-C_6)alkyl amino, di-(C_1-C_3)alkyl amino, or aminocarboxylate (i.e., (C_1-C_3)alkyl-O-C(O)-NH-), and more preferably, 1 or 2 substituents independently selected from (C_1-C_4)alkyl, chloro, fluoro, cyano, hydroxy, (C_1-C_4)alkoxy, (C_1-C_4)alkyl amino or di-(C_1-C_2)alkyl amino. The heteroaryl group may be attached to the chemical entity or moiety by any one of the atoms within the aromatic ring system (e.g., imidazol-1-yl, imidazol-2-yl, imidazol-4-yl, imidazol-5-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, pyrid-5-yl, or pyrid-6-yl). Similarly, the heteroaryl portion (i.e., heteroaromatic moiety) of a heteroaroyl or heteroaroyloxy (i.e., (heteroaryl)-C(O)-O-) has the same definition as above.

The term "acyl" refers to hydrogen, alkyl, partially saturated or fully saturated cycloalkyl, partially saturated or fully saturated heterocycle, aryl, and heteroaryl substituted carbonyl groups. For example, acyl includes groups such as (C_1-C_6)alkanoyl (e.g., formyl, acetyl, propionyl, butyryl, valeryl, caproyl, *t*-butylacetyl, etc.), (C_3-C_6)cycloalkylcarbonyl (e.g., cyclopropylcarbonyl,

cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, etc.), heterocyclic carbonyl (e.g., pyrrolidinylcarbonyl, pyrrolid-2-one-5-carbonyl, piperidinylcarbonyl, piperazinylcarbonyl, tetrahydrofuranylcarbonyl, etc.), aroyl (e.g., benzoyl) and heteroaroyl (e.g., thiophenyl-2-carbonyl, thiophenyl-3-carbonyl, furanyl-2-carbonyl, furanyl-3-carbonyl, 1H-pyrroyl-2-carbonyl, 1H-pyrroyl-3-carbonyl, benzo[b]thiophenyl-2-carbonyl, etc.). In addition, the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be any one of the groups described in the respective definitions above. When indicated as being "optionally substituted", unless specified otherwise, the acyl group may be unsubstituted or optionally substituted with one or more substituents (typically, one to three substituents) independently selected from the group of substituents listed below in the definition for "substituted" or the alkyl, cycloalkyl, heterocycle, aryl and heteroaryl portion of the acyl group may be substituted as described above in the preferred and more preferred list of substituents, respectively.

The term "substituted" specifically envisions and allows for one or more substitutions that are common in the art. However, it is generally understood by those skilled in the art that the substituents should be selected so as to not adversely affect the pharmacological characteristics of the compound or adversely interfere with the use of the medicament. Suitable substituents for any of the groups defined above include (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_2-C_6)alkenyl, (C_1-C_6)alkylidenyl, aryl, heteroaryl, 3- to 6-membered heterocycle, halo (e.g., chloro, bromo, iodo and fluoro), cyano, hydroxy, (C_1-C_6)alkoxy, phenoxy, sulfhydryl (mercapto), (C_1-C_6)alkylthio, phenylthio, amino, mono- or di-(C_1-C_6)alkyl amino, quaternary ammonium salts, amino(C_1-C_6)alkoxy, aminocarboxylate (i.e., (C_1-C_6)alkyl-O-C(O)-NH-), hydroxy(C_2-C_6)alkylamino, amino(C_1-C_6)alkylthio, cyanoamino, nitro, (C_1-C_6)carbamyl, keto (oxo), acyl, (C_1-C_6)alkyl-CO_2-, glycolyl, glycyl, hydrazino, guanyl, sulfamyl, sulfonyl, sulfinyl, thio(C_1-C_6)alkyl-C(O)-, thio(C_1-C_6)alkyl-CO_2-, and combinations thereof. In the case of substituted combinations, such as "substituted aryl(C_1-C_6)alkyl", either the aryl or the alkyl group may be substituted, or both the aryl and the alkyl groups may be substituted with one or more substituents (typically, one to three substituents except in the case of perhalo substitutions). A phenyl or heteroaryl substituted carbocyclic or heterocyclic group may be a fused ring (e.g., indanyl, dihydrobenzofuranyl, dihydroindolyl, etc.). A carbocyclic or heterocycle substituted phenyl or heteroaryl group may also be a fused ring.

The term "solvate" refers to a molecular complex of a compound represented by Formula (I) (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition, or disorder, (ii) attenuates, ameliorates, or eliminates one or more symptoms of the particular disease, condition,

or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition, or disorder described herein.

The term "animal" refers to humans (male or female), companion animals (e.g., dogs, cats and horses), food-source animals, zoo animals, marine animals, birds and other similar animal species. "Edible animals" refers to food-source animals such as cows, pigs, sheep and poultry. Preferably, the animal is human or a companion animal (preferably, the companion animal is a dog), more preferably, the animal is human (man and/or woman).

The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

The terms "treating", "treat", or "treatment" embrace both preventative, i.e., prophylactic, and palliative treatment.

The term "eating disorders" refer to illnesses in which the patient suffers disturbances in their eating behaviors and related thoughts and emotions. Representative examples of obesity-related eating disorders include overeating, bulimia, binge-eating disorder, compulsive dieting, nocturnal sleep-related eating disorder, pica, Prader-Willi Syndrome, and night-eating syndrome.

The terms "modulated by a cannabinoid receptor" or "modulation of a cannabinoid receptor" refers to the activation or deactivation of a cannabinoid receptor. For example, a ligand may act as an agonist, partial agonist, inverse agonist, antagonist, or partial antagonist.

The term "antagonist" includes both full antagonists and partial antagonists, as well as inverse agonists.

The term "CB-1 receptor" refers to the G-protein coupled type 1 cannabinoid receptor.

The term "compounds of the present invention" (unless specifically identified otherwise) refer to compounds of Formula (I), pharmaceutically acceptable salts of the compounds, and hydrates or solvates of the compounds, and/or salts, as well as, all stereoisomers (including diastereoisomers and enantiomers), tautomers and isotopically labeled compounds.

DETAILED DESCRIPTION

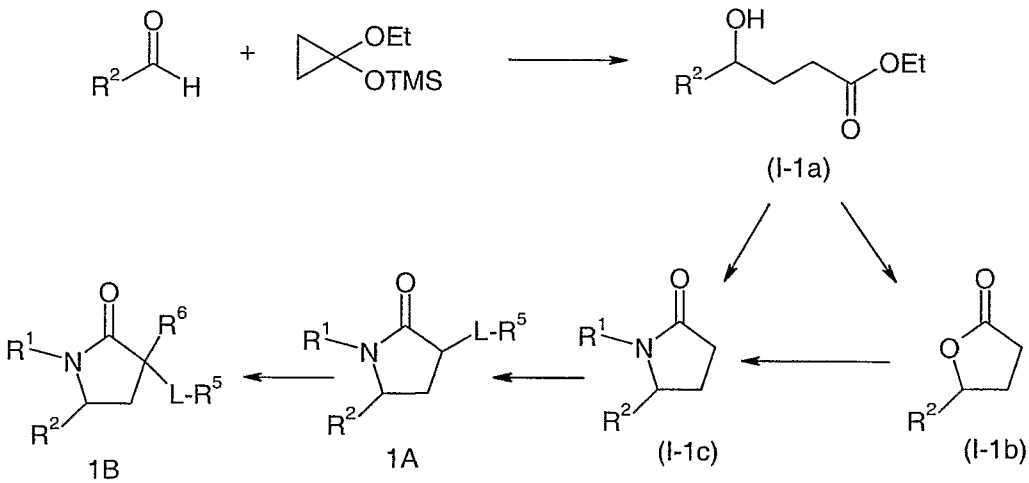
The present invention provides compounds and pharmaceutical formulations thereof that are useful in the treatment of diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists.

Compounds of the present invention may be synthesized by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, WI) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, Reagents for Organic Synthesis, v. 1-19, Wiley, New York (1967-1999 ed.), or Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available *via* the Beilstein online database)).

For illustrative purposes, the reaction schemes depicted below provide potential routes for synthesizing the compounds of the present invention as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents can be easily substituted to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the methods described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, *t*-butoxycarbonyl (BOC), benzyloxycarbonyl (CBz) and 9-fluorenylmethylenoxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable protecting groups include acetyl and silyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include $-CH_2CH_2SO_2Ph$, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(*p*-toluenesulfonyl)ethyl, 2-(*p*-nitrophenylsulfenyl)ethyl, 2-(diphenylphosphino)-ethyl, nitroethyl and the like. The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Scheme I outlines the general procedures for one approach one could use to provide compounds of the present invention.



Scheme I

Intermediate (I-1a) can be prepared by condensing an aldehyde having the desired functional group R^2 with 1-ethoxy-1-trimethylsiloxy-cyclopropane in the presence of a Lewis acid (e.g., titanium tetrachloride) in a reaction inert solvent (e.g., methylene chloride or chloroform) at a temperature from about 0ºC to about 50ºC. Under some conditions, the hydroxy ester (I-1a) may spontaneously cyclize to form the lactone intermediate (I-1b). If cyclization does not occur spontaneously, the cyclization can be accomplished by heating the hydroxy ester (I-1a) at a temperature from about 35ºC to about 150ºC with or without a solvent. Lactone (I-1b) can also be prepared by saponification of the hydroxy ester (I-1a) with an alkali metal hydroxide (e.g., sodium hydroxide or potassium hydroxide) in an aqueous solvent (e.g., water, a lower alcohol, such as methanol or ethanol, or a water/alcohol mixture) at a temperature from about 10ºC to about 50ºC. The resulting hydroxy acid may spontaneously cyclize to form the lactone (I-1b). Alternatively, the removal of water may be facilitated by heating (I-1a) at a temperature from about 35ºC to about 150ºC with or without a solvent, or by application of a dehydrating agent (e.g., magnesium sulfate or sodium sulfate).

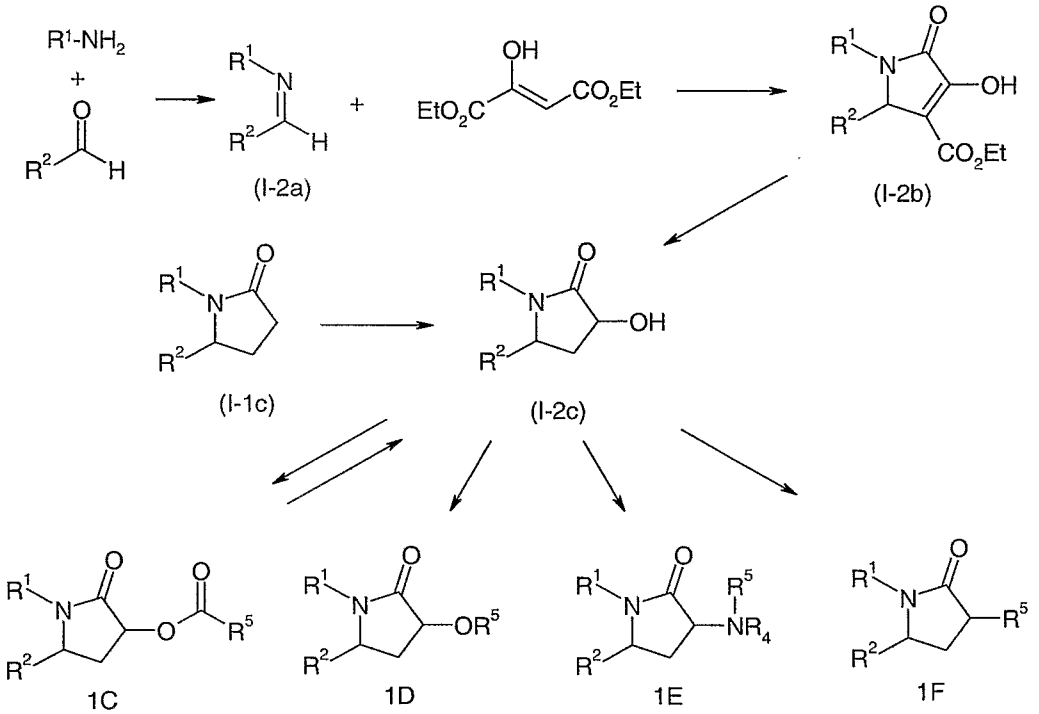
Intermediate (I-1c) can be prepared using procedures analogous to those described by Pernot, A., et al., Bull. Chim. Soc. Fr., 324-326 (1953). The lactam intermediate (I-1c) may be prepared from either the hydroxy ester intermediate (I-1a) or the lactone intermediate (I-1b) by reacting with a desired amino compound (R^1-NH_2) neat or in a reaction inert solvent at a temperature from about 50ºC to about 150ºC in the presence of a small amount of a strong acid (e.g., sulfuric or hydrochloric acid).

Compounds of Formula (I) in which L is alkyl, -C(O)-, -C(O)O-, -C(O)S-, -C(O)NH-, -C(O)N((C_1-C_7)alkyl)-, -CH_2C(O)-NH-, -CH_2C(O)-N((C_1-C_7)alkyl)-, or -CH(OH)- may be prepared by treating intermediate (I-1c) dissolved in a suitable solvent (e.g. tetrahydrofuran) with a strong base (e.g. lithium diisopropyl amide (LDA)) at a temperature from about 0ºC to about -78ºC. The enolate of intermediate (I-1c) so formed may then be treated with a suitably reactive alkyl derivative (e.g. alkyl chloride, alkyl bromide or alkyl iodide) at a temperature from about 50ºC to about -78ºC to produce compounds of Formula (I) wherein L is alkyl. Compounds of Formula (I) wherein L is -C(O)- may be prepared if the enolate of intermediate (I-1c) so formed is then be treated with a suitably reactive acid chloride (Cl-C(O)-R^5) or ester (RO-C(O)-R^5) at a temperature from about 50ºC to about -78ºC. Compounds of Formula (I) wherein L is -C(O)O- may be prepared if the enolate of intermediate (I-1c) so formed is then be treated with a suitably reactive carbonate (R^5O-C(O)-OR^5) or chloroformate (Cl-C(O)-OR^5) at a temperature from about 50ºC to about -78ºC. Compounds of Formula (I) wherein L is -C(O)S- may be prepared if the enolate of intermediate (I-1c) so formed is then be treated with a suitably reactive chloride (Cl-C(O)-SR^5) at a temperature from about 50ºC to about -78ºC. Compounds of Formula (I) wherein L is -C(O)NH- may be prepared if the enolate of intermediate (I-1c) so formed is then be treated with a suitably reactive isocyanate (OCN-R^5) at a temperature from about 50ºC to about -78ºC. Compounds of Formula (I) wherein L is -C(O)N((C_1-C_7)alkyl)- may be prepared if the enolate of

intermediate (I-1c) so formed is then be treated with a suitably reactive chloride (Cl-C(O)N((C$_1$-C$_7$)alkyl)R^5) at a temperature from about 50ºC to about -78ºC. Compounds of Formula (I) wherein L is -CH$_2$C(O)-NH- may be prepared if the enolate of intermediate (I-1c) so formed is then be treated with a suitably reactive derivative of formula XCH$_2$C(O)-NHR^5 wherein X is a leaving group (e.g. chloro, bromo, tosylate, or triflate) at a temperature from about 50ºC to about -78ºC. Compounds of Formula (I) wherein L is -CH(OH)- may be prepared if the enolate of intermediate (I-1c) so formed is then be treated with an aldehyde of formula R^{5}CHO at a temperature from about 50ºC to about -78ºC.

Compounds of Formula 1B in which R^6 is (C$_1$-C$_7$)alkyl may be prepared by treating compounds of Formula 1A with a strong base (e.g. LDA or sodium hydride) in a suitable solvent (e.g. THF) at a temperature from about 50ºC to about -78ºC. The enolate of compound 1A so formed may then be treated with a suitably reactive alkyl derivative (e.g. alkyl chloride, alkyl bromide or alkyl iodide) at a temperature from about 50ºC to about -78ºC to produce compounds of Formula (I) wherein R^5 is (C$_1$-C$_7$)alkyl.

Scheme II below outlines an alternative approach for making compounds of the present invention, in particular those wherein L is O, OCH$_2$, OC(O), NR^4 or a bond.



Scheme II

Intermediates (I-2b) and (I-2c) can be prepared by methods analogous to those described by Wasserman, H. H.; Koch, R. C. *J. Org. Chem.*, **1962**, *27*, 35-39. Mixing an amine R1-NH2 with an aldehyde R^2-CHO in a suitable solvent (e.g. ethanol) produces intermediate (I-2a). In some cases, the preparation of (I-2a) may be hastened by removal of water from the reaction medium, for example by heating an amine R1-NH$_2$ with an aldehyde R^2-CHO is a suitable solvent (e.g. benzene or toluene), preferably with the aid of equipment such as a Dean-

Stark apparatus. Reaction of compound (I-2a) with diethyl oxalacetate in a suitable solvent (e.g. acetic acid or ethyl ether) gives intermediate (I-2b). Intermediate (I-2c) can be prepared by treating intermediate (I-2b) with a strong mineral acid, such as hydrochloric or hydroiodic acid, and a reducing agent, preferably sodium hypophosphite, in a suitable solvent, preferably acetic acid, at a temperature from about 100ºC to about 30ºC.

Intermediate (I-2c) may also be prepared by treating intermediate (I-1c) with a strong base (e.g. LDA or sodium hydride) in a suitable solvent (e.g. THF) at a temperature from about 25ºC to about -78ºC. The enolate of intermediate (I-1c) so formed may then be treated with a suitably reactive oxygenating agent (e.g. 2-(phenylsulfonyl)-3-phenyloxaziridine, Davis, F.A., *et al. Org. Syn.*,**1987**, *66*, 203-210) at a temperature from about 25ºC to about -78ºC to produce intermediate (I-2c).

Compounds of Formula (I) wherein L is –OC(O)- (i.e. compounds 1C) can be prepared by treating (I-2c) with an acid chloride R^5-C(O)Cl in a suitable solvent (e.g. methylene chloride, THF or pyridine) with an amine base (e.g. triethyl amine or 4-(N,N-dimethylamino)pyridine or both) at a temperature from about 30ºC to about -20ºC. Another method of producing compounds 1C involves treating (I-2c) with a mixture of carboxylic acid R^5-CO_2H, triphenyl phosphine and diethyl- or diisopropylazodicarboxylate in a solvent such as methylene chloride or THF at a temperature from about 70ºC to about -10ºC.

Examples of compounds of Formula (I) wherein L is –OC(O)- (i.e. compounds 1C) and R^5 is an optically active moiety are also useful for preparing the stereoisomers of intermediate (I-2c). If intermediate (I-2c) is racemic and the acid chloride R^5-C(O)Cl or the acid R-CO_2H in the methods described above is optically active, the compounds 1C so produced are mixtures of diastereomers which may be separated by ordinary chromatographic or cryallographic methods known to those skilled in the art. Examples of suitable optically active acids include derivatized amino acids (e.g. Boc-alanine or Boc-phenylalanine or Boc-proline) or camphanic acid. The compounds 1C obtained in this way are a single stereoisomer and may be used to prepare intermediate (I-2c) with a single stereoisomeric configuration by treatment with an a mild base (e.g. KOH, NaOH, LiOH) in a suitable solvent such as water or a lower alcohol (e.g. methanol or ethanol) or a mixture of water and a lower alcohol at a temperature from about 80ºC to about 20ºC. The optically active intermediate (I-2c) is useful for preparing optically active examples of compounds of Formula (I).

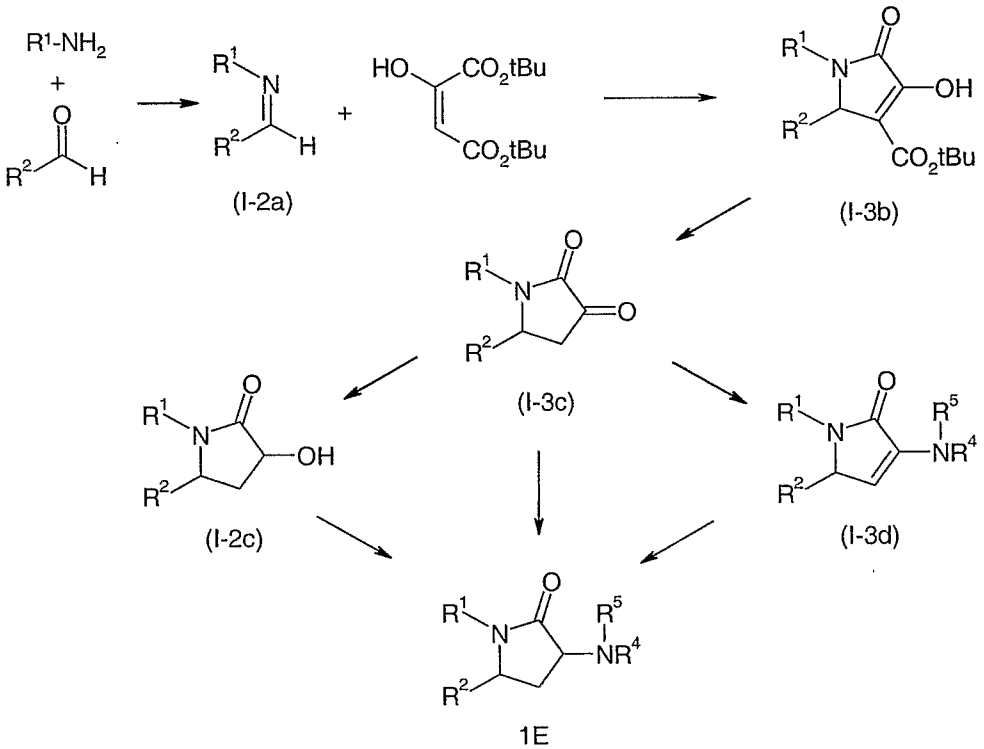
Compounds of Formula (I) wherein L is O (i.e. compounds 1D) and R^5 is (C_1-C_8)alkyl or (C_1-C_4)alkylaryl may be prepared by treating intermediate (I-2c) with a strong base (e.g. sodium hydride) and a (C_1-C_8)alkyl halide or (C_1-C_4)alkylaryl halide wherein the halide is chloro, bromo or iodole in a suitable solvent (e.g. THF or DMF) at a temperature from about 100ºC to about 0ºC.

Compounds of Formula (I) wherein L is O (i.e. compounds 1D) and R^5 is aryl may be prepared by treating intermediate (I-2c) with an aryl-OH and triphenyl phosphine and diethyl- or diisopropylazodicarboxylate in a solvent such as methylene chloride or THF at a temperature from about 80ºC to about 20ºC.

Compounds of Formula (I) wherein L is -NR^4 (i.e. compounds 1E) may be prepared by first converting intermediate (I-2c) into an activated derivative such as the methanesulfonate, toluenesulfonate, trifluoromethanesulfonate (triflate) by treatment with methanesulfonyl chloride, toluenesulfonyl chloride or triflic anhydride, respectively, and a mild tertiary amine base (e.g. triethylamine) in a solvent such as methylene chloride or THF at a temperature from about 40ºC to about -10ºC. Other activated derivates of intermediate (I-2c) include the corresponding halides (e.g. bromide) which may be prepared by treating (I-2c) with a reagent such as BBr_3 or PBr_3. In a second step, the activated derivative of (I-2c) so formed is then treated with an amine of formula HNR4R5 in a suitable solvent (e.g. THF or DMF) at a temperature from about 100ºC to about 0ºC.

Compounds of Formula (I) wherein L is a bond and R^5 is heteroaryl or a 3-6 membered partially or fully saturated heterocycle (i.e. compounds 1F may be prepared by treating the activated derivative of (I-2c) described above with an appropriate aromatic heterocycle or a 3-6 membered partially or fully saturated heterocycle containing a substitutable NH with or without a base such as triethyl amine or sodium hydride in a solvent such as THF or DMF at a temperature from about 100ºC to about 0ºC.

Scheme III outlines an alternative approach for making compounds of the present invention, in particular those wherein L is –NR^4.



Scheme III

Intermediate (I-3b) may be prepared using methods analogous to those described for the preparation of (I-2b) and Scheme II. Mixing an amine R^1-NH_2 with an aldehyde R^2-CHO in a suitable solvent (e.g. ethanol) produces intermediate (I-2a). In some cases, the preparation of (I-

2a) may be hastened by removal of water from the reaction medium, for example by heating an amine R^1-NH_2 with an aldehyde R^2-CHO is a suitable solvent (e.g. benzene or toluene), preferably with the aid of equipment such as a Dean-Stark apparatus. Reaction of compound (I-2a) with di-t-butyl oxalacetate (Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.*, **1983**, *48*, 5017-5022) in a suitable solvent (e.g. ethyl ether or toluene) gives intermediate (I-3b). Intermediate (I-3c) can be prepared by treating intermediate (I-3b) with a strong mineral acid such as gaseous hydrochloric acid dissolved in a suitable solvent (e.g. chloroform or ethyl acetate) or with a strong carboxylic acid (e.g. trifluoroacetic acid) either alone or dissolved in a solvent (e.g. chloroform) at a temperature from about 80ºC to about 0ºC.

Intermediate (I-3c) may be used to prepare intermediate (I-2c) by the action of a mild reducing agent (e.g. sodium borohydride) in a suitable solvent (e.g. methanol or ethanol) at a temperature from about 50ºC to about 0ºC.

Compounds of Formula (I) wherein L is -NR^4 (compounds 1E) may be prepared by treating intermediate (I-3c) with an amine HNR^4R^5 and a mild reducing agent (e.g. sodium cyanoborohydride or sodium triacetoxyborohydride) in a suitable solvent (e.g. methanol or ethanol) at a temperature from about 50ºC to about 0ºC. Compounds 1E may also be prepared by reacting intermediate (I-3c) with an amine $H_2NR^4R^5$ with the removal of water to form intermediate (I-3d) as the first step. Examples of methods to remove water include heating the reagents in a solvent such as benzene or toluene at a temperature from about 75ºC to about 110ºC. The use of an equipment such as a Dean-Stark apparatus may be beneficial. In a second step, the intermediate (I-3d) may be converted into compounds 1E by the action of a mild reducing agent (e.g. sodium borohydride or sodium cyanoborohydride) in a suitable solvent (e.g. methanol, ethanol, acetic acid or water or a combination of solvents) at a temperature from about 50ºC to about 0ºC.

Conventional methods and/or techniques of separation and purification known to one of ordinary skill in the art can be used to isolate the compounds of the present invention, as well as the various intermediates related thereto. Such techniques will be well known to one of ordinary skill in the art and may include, for example, all types of chromatography (high pressure liquid chromatography (HPLC), column chromatography using common adsorbents such as silica gel, and thin-layer chromatography), recrystallization, and differential (i.e., liquid-liquid) extraction techniques.

The compounds of the present invention may be isolated and used *per se* or in the form of its pharmaceutically acceptable salt, solvate and/or hydrate. The term "salts" refers to inorganic and organic salts of a compound of the present invention. These salts can be prepared *in situ* during the final isolation and purification of a compound, or by separately reacting the compound, N-oxide, or prodrug with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, hydroiodide, sulfate, bisulfate, nitrate, acetate, trifluoroacetate, oxalate, besylate, palmitiate, pamoate, malonate, stearate, laurate, malate, borate, benzoate, lactate, phosphate, hexafluorophosphate, benzene

sulfonate, tosylate, formate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to, ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. See, e.g., Berge, et al., *J. Pharm. Sci.*, **66**, 1-19 (1977).

In the practice of the present invention, it may be useful to utilize a prodrug (also referred to as "esters"). The term "prodrug" means a compound that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. Prodrugs are also referred to as "esters." The transformation may occur by various mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as $(C_1$-$C_8)$alkyl, $(C_2$-$C_{12})$alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1$-$C_2)$alkylamino$(C_2$-$C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1$-$C_2)$alkyl, N,N-di$(C_1$-$C_2)$alkylcarbamoyl-$(C_1$-$C_2)$alkyl and piperidino-, pyrrolidino- or morpholino$(C_2$-$C_3)$alkyl.

Similarly, if a compound of the present invention contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as $(C_1$-$C_6)$alkanoyloxymethyl, 1-$((C_1$-$C_6)$alkanoyloxy)ethyl, 1-methyl-1-$((C_1$-$C_6)$alkanoyloxy)ethyl, $(C_1$-$C_6)$alkoxycarbonyloxymethyl, N-$(C_1$-$C_6)$alkoxycarbonylaminomethyl, succinoyl, $(C_1$-$C_6)$alkanoyl, α-amino$(C_1$-$C_4)$alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $P(O)(O(C_1$-$C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

If a compound of the present invention incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently $(C_1$-$C_{10})$alkyl, $(C_3$-$C_7)$cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-

aminoacyl-natural α-aminoacyl, -C(OH)C(O)OY' wherein Y' is H, (C_1-C_6)alkyl or benzyl, -C(OY_0)Y_1 wherein Y_0 is (C_1-C_4) alkyl and Y_1 is (C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl, -C(Y_2)Y_3 wherein Y_2 is H or methyl and Y_3 is mono-N- or di-N,N-(C_1-C_6)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

The compounds of the present invention may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the present invention as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of the present invention incorporates a double bond or a fused ring, both the *cis*- and *trans*- forms, as well as mixtures, are embraced within the scope of the invention.

Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of a chiral HPLC column.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms.

It is also possible that the compounds of the present invention may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible *via* a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions *via* migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

The present invention also embraces isotopically-labeled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{123}I, ^{125}I and ^{36}Cl, respectively.

Certain isotopically-labeled compounds of the present invention (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e.,

^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as ^{15}O, ^{13}N, ^{11}C, and ^{18}F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

Compounds of the present invention are useful for treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists; therefore, another embodiment of the present invention is a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention and a pharmaceutically acceptable excipient, diluent or carrier.

A typical formulation is prepared by mixing a compound of the present invention and a carrier, diluent or excipient. Suitable carriers, diluents and excipients are well known to those skilled in the art and include materials such as carbohydrates, waxes, water soluble and/or swellable polymers, hydrophilic or hydrophobic materials, gelatin, oils, solvents, water, and the like. The particular carrier, diluent or excipient used will depend upon the means and purpose for which the compound of the present invention is being applied. Solvents are generally selected based on solvents recognized by persons skilled in the art as safe (GRAS) to be administered to a mammal. Suitable aqueous solvents include water, ethanol, propylene glycol, polyethylene glycols (e.g., PEG400, PEG300), etc. and mixtures thereof. Other known additives may be added to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

The formulations may be prepared using conventional dissolution and mixing procedures. For example, the bulk drug substance (i.e., compound of the present invention or stabilized form of the compound (e.g., complex with a cyclodextrin derivative or other known complexation agent)) is dissolved in a suitable solvent in the presence of one or more of the excipients described above. The compound of the present invention is typically formulated into pharmaceutical dosage forms to provide an easily controllable dosage of the drug and to give the patient an elegant and easily handleable product.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent

indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

The present invention further provides a method of treating diseases, conditions and/or disorders modulated by cannabinoid receptor antagonists in an animal that includes administering to an animal in need of such treatment a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition comprising an effective amount of a compound of the present invention and a pharmaceutically acceptable excipient, diluent, or carrier. The method is particularly useful for treating diseases, conditions and/or disorders modulated by cannabinoid receptor (in particular, CB1 receptor) antagonists.

Preliminary investigations have indicated that the following diseases, conditions, and/or disorders are modulated by cannabinoid receptor antagonists: eating disorders (in particular, obesity-related eating disorders such as overeating, bulimia, binge-eating disorder, compulsive dieting, nocturnal sleep-related eating disorder, pica, Prader-Willi Syndrome, and night-eating syndrome), weight loss or control (e.g., reduction in calorie or food intake, and/or appetite suppression), obesity, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors (e.g., conditioned place avoidance, such as suppression of cocaine- and morphine-induced conditioned place preference), substance abuse, addictive disorders, impulsivity, alcoholism (e.g., alcohol abuse, addiction and/or dependence including treatment for abstinence, craving reduction and relapse prevention of alcohol intake), tobacco abuse (e.g., smoking addiction, cessation and/or dependence including treatment for craving reduction and relapse prevention of tobacco smoking), dementia (including memory loss, Alzheimer's disease, dementia of aging, vascular dementia, mild cognitive impairment, age-related cognitive decline, and mild neurocognitive disorder), sexual dysfunction in males (e.g., erectile difficulty), seizure disorders, epilepsy, inflammation, gastrointestinal disorders (e.g., dysfunction of gastrointestinal motility or intestinal propulsion), attention deficit disorder (ADD including attention deficit hyperactivity disorder (ADHD)), a deficiency in attention and/or cognition, Parkinson's disease, and type II diabetes. Consequently, the compounds of the present invention (including the compositions and processes used therein) may be used in the manufacture of a medicament for the therapeutic applications described herein.

As used herein, the phrase "deficiency in attention and/or cognition" refers to a subnormal functioning in one or more cognitive aspects such as memory, intellect, or learning and logic ability, in a particular individual relative to other individuals within the same general age population. "Deficiency in attention and/or cognition" also refers to a reduction in any particular individual's functioning in one or more cognitive aspects.

Preferred indications include obesity and obesity-related eating disorders, attention or cognitive deficit disorders, Parkinson's disease, dementia, alcoholism, tobacco abuse and inflammation.

Other diseases, conditions and/or disorders for which cannabinoid receptor antagonists may be effective include: premenstrual syndrome or late luteal phase syndrome, migraines, panic disorder, anxiety, post-traumatic syndrome, social phobia, cognitive impairment in non-demented individuals, non-amnestic mild cognitive impairment, post operative cognitive decline, disorders associated with impulsive behaviours (such as, disruptive behaviour disorders (e.g., anxiety/depression, executive function improvement, tic disorders, conduct disorder and/or oppositional defiant disorder), adult personality disorders (e.g., borderline personality disorder and antisocial personality disorder), diseases associated with impulsive behaviours (e.g., substance abuse, paraphilias and self-mutilation), and impulse control disorders (e.g., intermittene explosive disorder, kleptomania, pyromania, pathological gambling, and trichotillomania)), obsessive compulsive disorder, chronic fatigue syndrome, sexual dysfunction in males (e.g., premature ejaculation), sexual dysfunction in females, disorders of sleep (e.g., sleep apnea), autism, mutism, neurodengenerative movement disorders, spinal cord injury, damage of the central nervous system (e.g., trauma), stroke, neurodegenerative diseases or toxic or infective CNS diseases (e.g., encephalitis or meningitis), cardiovascular disorders (e.g., thrombosis), and diabetes.

The compounds of the present invention can be administered to a patient at dosage levels in the range of from about 0.7 mg to about 7,000 mg per day. For an adult human having a body weight of about 70 kg, a dosage in the range of from about 0.01 mg to about 100 mg per kilogram body weight is typically sufficient. However, some variability in the general dosage range may be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular compound being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure. It is also noted that the compounds of the present invention can be used in sustained release, controlled release, and delayed release formulations, which forms are also well known to one of ordinary skill in the art.

The compounds of this invention may also be used in conjunction with other pharmaceutical agents for the treatment of the diseases, conditions and/or disorders described herein. Therefore, methods of treatment that include administering compounds of the present invention in combination with other pharmaceutical agents are also provided. Suitable pharmaceutical agents that may be used in combination with the compounds of the present invention include anti-obesity agents such as apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, 11β-hydroxy steroid dehydrogenase-1 (11β-HSD type 1) inhibitors, peptide YY_{3-36} or analogs thereof, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (such as sibutramine), opioid antagonists, sympathomimetic agents, β_3 adrenergic receptor agonists, dopamine agonists (such as bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor

agonists, galanin antagonists, lipase inhibitors (such as tetrahydrolipstatin, i.e. orlistat), anorectic agents (such as a bombesin agonist), Neuropeptide-Y receptor antagonists (e.g., NPY Y5 receptor antagonists, such as the spiro compounds described in US Patent Nos. 6,566,367; 6,649,624; 6,638,942; 6,605,720; 6,495,559; 6,462,053; 6,388,077; 6,335,345; and 6,326,375; US Publication Nos. 2002/0151456 and 2003/036652; and PCT Publication Nos. WO 03/010175. WO 03/082190 and WO 02/048152), thyromimetic agents, dehydroepiandrosterone or an analog thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (such as Axokine™ available from Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Procter & Gamble Company, Cincinnati, OH), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists and the like. Other anti-obesity agents, including the preferred agents set forth hereinbelow, are well known, or will be readily apparent in light of the instant disclosure, to one of ordinary skill in the art.

Especially preferred are anti-obesity agents selected from the group consisting of orlistat, sibutramine, bromocriptine, ephedrine, leptin, pseudoephedrine; peptide YY_{3-36} or an analog thereof; opioid antagonists, and 2-oxo-N-(5-phenylpyrazinyl)spiro-[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide. Preferably, compounds of the present invention and combination therapies are administered in conjunction with exercise and a sensible diet.

Representative anti-obesity agents for use in the combinations, pharmaceutical compositions, and methods of the invention can be prepared using methods known to one of ordinary skill in the art, for example, sibutramine can be prepared as described in U.S. Pat. No. 4,929,629; bromocriptine can be prepared as described in U.S. Pat. Nos. 3,752,814 and 3,752,888; orlistat can be prepared as described in U.S. Pat. Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874; PYY_{3-36} (including analogs) can be prepared as described in US Publication No. 2002/0141985 and WO 03/027637; and the NPY Y5 receptor antagonist 2-oxo-N-(5-phenylpyrazinyl)spiro[isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide can be prepared as described in US Publication No. 2002/0151456. Other useful NPY Y5 receptor antagonists include those described in PCT Publication No. 03/082190, such as 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H), 4'-piperidine]-1'-carboxamide; 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)-spiro-[isobenzofuran-1(3H), 4'-piperidine]-1'-carboxamide; N- [5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-[isobenzofuran-1(3H), [4'-piperidine]-1'-carboxamide; *trans*-3'-oxo-N-(5-phenyl-2-pyrimidinyl)] spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide; *trans*-3'-oxo-N- [1-(3-quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide; *trans*-3-oxo-N-(5-phenyl-2-pyrazinyl)spiro[4-azaiso-benzofuran-1(3H),1'-cyclohexane]-4'-carboxamide; *trans*-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H), 1′-cyclohexane]-4′-carboxamide; *trans*-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H), 1′-cyclohexane]-4′-carboxamide; *trans*-N-[1-(3,5-difluorophenyl)-4-imidazolyl]-3-oxospiro[7-azaisobenzofuran-

1(3H),1′-cyclohexane]-4'-carboxamide; *trans*-3-oxo-N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1′-cyclohexane]-4′-carboxamide; *trans*-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1′-cyclohexane]-4′-carboxamide; *trans*-3-oxo-N-(l-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1′-cyclohexane]-4′-carboxamide; *trans*-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-azaisobenzofuran-1(3H),1′-cyclohexane]-4′-carboxamide; and pharmaceutically acceptable salts and esters thereof. All of the above recited U.S. patents and publications are incorporated herein by reference.

Other suitable pharmaceutical agents that may be administered in combination with the compounds of the present invention include agents designed to treat tobacco abuse (e.g., nicotine receptor partial agonists, bupropion hypochloride (also known under the tradename Zyban™) and nicotine replacement therapies), agents to treat erectile dysfunction (e.g., dopaminergic agents, such as apomorphine), antipsychotic agents (e.g., Chlorpromazine, Fluphenazine, Haloperidol, Loxapine, Mesoridazine, Molindone, Perphenazine, Pimozide, Thioridazine, Thiothixene, Trifluoperazine, Asenapine, Ziprasidone, Olanzapine, Clozapine, Risperidone, Sertindole, Quetiapine, Aripiprazole or Amisulpride). ADD/ADHD agents (e.g., Ritalin™, Strattera™, Concerta™ and Adderall™), and agents to treat alcoholism, such as opioid antagonists (e.g., naltrexone (also known under the tradename ReVia™) and nalmefene), disulfiram (also known under the tradename Antabuse™), and acamprosate (also known under the tradename Campral™)). In addition, agents for reducing alcohol withdrawal symptoms may also be co-administered, such as benzodiazepines, beta-blockers, clonidine, carbamazepine, pregabalin, and gabapentin (Neurontin™).

Treatment for alcoholism is preferably administered in combination with behavioral therapy including such components as motivational enhancement therapy, cognitive behavioral therapy, and referral to self-help groups, including Alcohol Anonymous (AA).

Other suitable pharmaceutical agents include antihypertensive agents; anti-inflammatory agents (e.g., COX-2 inhibitors); antidepressants (e.g., fluoxetine hydrochloride (Prozac™)); cognitive improvement agents (e.g., donepezil hydrochloride (Aircept™) and other acetylcholinesterase inhibitors); neuroprotective agents (e.g., memantine); antipsychotic medications (e.g., ziprasidone (Geodon™), risperidone (Risperdal™), and olanzapine (Zyprexa™)); insulin and insulin analogs (e.g., LysPro insulin); GLP-1 (7-37) (insulinotropin) and GLP-1 (7-36)-NH_2; sulfonylureas and analogs thereof: chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, Glypizide®, glimepiride, repaglinide, meglitinide; biguanides: metformin, phenformin, buformin; □2-antagonists and imidazolines: midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan; other insulin secretagogues: linogliride, A-4166; glitazones: ciglitazone, Actos® (pioglitazone), englitazone, troglitazone, darglitazone, Avandia® (BRL49653); fatty acid oxidation inhibitors: clomoxir, etomoxir; □-glucosidase inhibitors: acarbose, miglitol, emiglitate, voglibose, MDL-25,637, camiglibose, MDL-73,945; □-agonists: BRL 35135, BRL 37344, RO 16-8714, ICI D7114, CL 316,243; phosphodiesterase

inhibitors: L-386,398; lipid-lowering agents: benfluorex: fenfluramine; vanadate and vanadium complexes (e.g., Naglivan®) and peroxovanadium complexes; amylin antagonists; glucagon antagonists; gluconeogenesis inhibitors; somatostatin analogs; antilipolytic agents: nicotinic acid, acipimox, WAG 994, pramlintide (Symlin□), AC 2993, nateglinide, aldose reductase inhibitors (e.g., zopolrestat), glycogen phosphorylase inhibitors, sorbitol dehydrogenase inhibitors, sodium-hydrogen exchanger type 1 (NHE-1) inhibitors and/or cholesterol biosynthesis inhibitors or cholesterol absorption inhibitors, especially a HMG-CoA reductase inhibitor (e.g., atorvastatin or the hemicalcium salt thereof), or a HMG-CoA synthase inhibitor, or a HMG-CoA reductase or synthase gene expression inhibitor, a CETP inhibitor, a bile acid sequesterant, a fibrate, an ACAT inhibitor, a squalene synthetase inhibitor, an anti-oxidant or niacin. The compounds of the present invention may also be administered in combination with a naturally occurring compound that acts to lower plasma cholesterol levels. Such naturally occurring compounds are commonly called nutraceuticals and include, for example, garlic extract, *Hoodia* plant extracts, and niacin.

The dosage of the additional pharmaceutical agent is generally dependent upon a number of factors including the health of the subject being treated, the extent of treatment desired, the nature and kind of concurrent therapy, if any, and the frequency of treatment and the nature of the effect desired. In general, the dosage range of the additional pharmaceutical agent is in the range of from about 0.001 mg to about 100 mg per kilogram body weight of the individual per day, preferably from about 0.1 mg to about 10 mg per kilogram body weight of the individual per day. However, some variability in the general dosage range may also be required depending upon the age and weight of the subject being treated, the intended route of administration, the particular anti-obesity agent being administered and the like. The determination of dosage ranges and optimal dosages for a particular patient is also well within the ability of one of ordinary skill in the art having the benefit of the instant disclosure.

According to the methods of the invention, a compound of the present invention or a combination of a compound of the present invention and at least one additional pharmaceutical agent is administered to a subject in need of such treatment, preferably in the form of a pharmaceutical composition. In the combination aspect of the invention, the compound of the present invention and at least one other pharmaceutical agent (e.g., anti-obesity agent, nicotine receptor partial agonist, dopaminergic agent, or opioid antagonist) may be administered either separately or in the pharmaceutical composition comprising both. It is generally preferred that such administration be oral. However, if the subject being treated is unable to swallow, or oral administration is otherwise impaired or undesirable, parenteral or transdermal administration may be appropriate.

When a combination of a compound of the present invention and at least one other pharmaceutical agent are administered together, such administration can be sequential in time or simultaneous with the simultaneous method being generally preferred. For sequential administration, a compound of the present invention and the additional pharmaceutical agent can be administered in any order. It is generally preferred that such administration be oral. It is

especially preferred that such administration be oral and simultaneous. When a compound of the present invention and the additional pharmaceutical agent are administered sequentially, the administration of each can be by the same or by different methods.

Compositions suitable for parenteral injection generally include pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions, or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions.

Solid dosage forms for oral administration include capsules, tablets, powders, and granules. In such solid dosage forms, a compound of the present invention or a combination is admixed with at least one inert excipient, diluent or carrier. Suitable excipients, diluents or carriers include materials such as sodium citrate or dicalcium phosphate or (a) fillers or extenders (e.g., starches, lactose, sucrose, mannitol, silicic acid and the like); (b) binders (e.g., carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, acacia and the like); (c) humectants (e.g., glycerol and the like); (d) disintegrating agents (e.g., agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, sodium carbonate and the like); (e) solution retarders (e.g., paraffin and the like); (f) absorption accelerators (e.g., quaternary ammonium compounds and the like); (g) wetting agents (e.g., cetyl alcohol, glycerol monostearate and the like); (h) adsorbents (e.g., kaolin, bentonite and the like); and/or (i) lubricants (e.g., talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate and the like). In the case of capsules and tablets, the dosage forms may also comprise buffering agents. Solid compositions of a similar type may also be used as fillers in soft or hard filled gelatin capsules using such excipients as lactose or milk sugar, as well as high molecular weight polyethylene glycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They may also contain opacifying agents, and can also be of such composition that they release the compound of the present invention and/or the additional pharmaceutical agent in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The drug can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the compound of the present invention or the combination, the liquid dosage form may contain inert diluents commonly used in the art. Suspensions, in addition to the compound of the present invention or the combination, may further comprise carriers such as suspending agents.

Embodiments of the present invention are illustrated by the following Examples. It is to be understood, however, that the embodiments of the invention are not limited to the specific details of these Examples, as other variations thereof will be known, or apparent in light of the instant disclosure, to one of ordinary skill in the art.

EXAMPLES

Unless specified otherwise, starting materials are generally available from commercial sources such as Aldrich Chemicals Co. (Milwaukee, WI), Lancaster Synthesis, Inc. (Windham, NH), Acros Organics (Fairlawn, NJ), Maybridge Chemical Company, Ltd. (Cornwall, England), Tyger Scientific (Princeton, NJ), and AstraZeneca Pharmaceuticals (London, England).

General Experimental Procedures

NMR spectra were recorded on a Varian Unity™ 400 or 500 (available from Varian Inc., Palo Alto, CA) at room temperature at 400 and 500 MHz ^{1}H, respectively. Chemical shifts are expressed in parts per million (δ) relative to residual solvent as an internal reference. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet; v br s, very broad singlet; br m, broad multiplet; 2s, two singlets. In some cases only representative ^{1}H NMR peaks are given.

Mass spectra were recorded by direct flow analysis using positive and negative atmospheric pressure chemical ionization (APcI) scan modes. A Waters APcI/MS model ZMD mass spectrometer equipped with Gilson 215 liquid handling system was used to carry out the experiments

Mass spectrometry analysis was also obtained by RP-HPLC gradient method for chromatographic separation. Molecular weight identification was recorded by positive and negative electrospray ionization (ESI) scan modes. A Waters/Micromass ESI/MS model ZMD or LCZ mass spectrometer equipped with Gilson 215 liquid handling system and HP 1100 DAD was used to carry out the experiments.

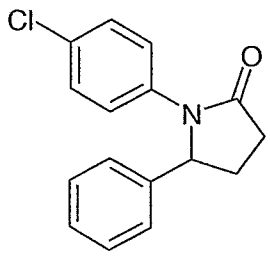
Where the intensity of chlorine or bromine-containing ions are described, the expected intensity ratio was observed (approximately 3:1 for ^{35}Cl/^{37}Cl-containing ions and 1:1 for ^{79}Br/^{81}Br-containing ions) and only the lower mass ion is given. MS peaks are reported for all examples.

Optical rotations were determined on a PerkinElmer™ 241 polarimeter (available from PerkinElmer Inc., Wellesley, MA) using the sodium D line (λ = 589 nm) at the indicated temperature and are reported as follows $[\alpha]_D^{temp}$, concentration (c = g/100 ml), and solvent.

Column chromatography was performed with either Baker™ silica gel (40 μm; J.T. Baker, Phillipsburg, NJ) or Silica Gel 50 (EM Sciences™, Gibbstown, NJ) in glass columns or in Biotage™ columns (ISC, Inc., Shelton, CT) under low nitrogen pressure or in RediSep™ columns (ISCO, Inc., Lincoln, NE).

Key Intermediates

Preparation of Intermediate 1-(4-chloro-phenyl)-5-phenyl-pyrrolidin-2-one (I-1a):



I-1a

A mixture of 2.0 g (12.3 mmol) of 5-phenyl butyrolactone, 6.9 g (54 mmol) of 4-chloroaniline and 3.4 g (21 mmol) of 4-chloroaniline hydrochloride under nitrogen was heated at 180°C (external temperature, sand bath) for 4 hours. The mixture was cooled to room temperature and poured into 50 ml of 1M HCl, diluted with water and extracted with methylene chloride. The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by silica gel MPLC with chloroform gave 0.60 g (46%) of the title compound (I-1a). ^{1}H NMR ($CDCl_3$): δ 2.0 (m, 1H), 2.55-2.8 (m, 3H), 5.21 (dd, J = 7.5, 4.6, 1H), 7.1-7.5 (m, 9H).

The following intermediates were prepared using procedures analogous to those described above for the synthesis of intermediate I-1a using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

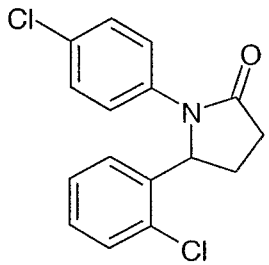
1-(4-chloro-phenyl)-5-(4-chloro-phenyl)-pyrrolidin-2-one (I-1b)

1-(2-chloro-phenyl)-5-(2-chloro-phenyl)-pyrrolidin-2-one (I-1c)

1-(2-chloro-phenyl)-5-(4-chloro-phenyl)-pyrrolidin-2-one (I-1d)

1-(4-chloro-phenyl)-5-(2-chloro-phenyl)-pyrrolidin-2-one (I-2a)

Preparation of Intermediate 1-(4-chloro-phenyl)-5-(2-chloro-phenyl)-pyrrolidin-2-one (I-2a):



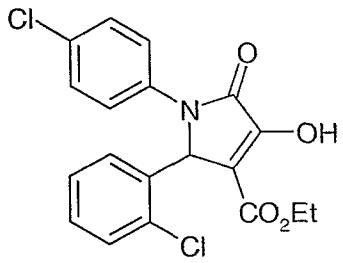
I-2a

A solution of 5.0 g (36 mmol) of 2-chlorobenzaldehyde in 70 ml dry methylene chloride under nitrogen atmosphere was chilled to -78°C and titanium tetrachloride was added (39 ml, 1.0 M in methlene chloride). A solution of 8.6 ml (43 mmol) of [(1-ethoxycyclo-propyl)oxy]trimethylsilane in 25 ml dry methylene chloride was added over 10 minutes. After 20 minutes, the reaction was allowed to warm to 0°C for 1 hour and allowed to warm to room temperature overnight. The mixture was poured into 100 ml of satd ammonium chloride, the layers were separated and the aqueous phase extracted with methylele chloride (2x). The combined organic layers were dried (magnesium sulfate), filtered and evaportated to give 8.7 g (100%) of ethyl 4-(2-chloro-phenyl)-4-hydroxy-butyrate of sufficient purity for use in the next step.

Ethyl 4-(2-chloro-phenyl)-4-hydroxy-butyrate (9.9 g, 41 mmol) and 7.8 g (61 mmol) of 2-chloroaniline were heated under nitrogen until the mixture melted. Seven drops of concentrated sulfuric acid was added carefully, and the mixture heated at 180°C (external temperature, sand bath) for 4 hours. The mixture was cooled to room temperature, dissolved in methylene chloride

and washed with 1M HCl. The organic layer was dried (magnesium sulfate), filtered and evaporated. Purification by silica gel MPLC with chloroform gave 5.63 g (45%) of the title compound (I-2a). MH+ 307. ^{1}H NMR ($CDCl_3$): δ2.05 (m, 1H), 2.6-2.85 (m, 3H), 5.76 (dd, J = 7.6, 5.6, 1H), 7.1-7.5 (m, 8H).

Preparation of Intermediate ethyl 5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3a):



I-3a

A solution of 20.0 g (142 mmol) of 2- chlorobenzaldehyde and 18.2 g (142 mmol) of 4-chloroaniline in 200 ml of absolute ethanol was stirred at room temperature for 16 hours. The solvent was evaporated, the residue was triturated with i-PrOH and collected by filtration to give 33.7 g (95%) of imine.

A solution of 31.1 g (148 mmol) of diethyloxalacetate sodium salt in water was layered with ether and acidified with concentrated sulfuric acid. After agitation, the layers were separated and the aqueous phase extracted twice more with ether. The combined organic layers were dried (magnesium sulfate) and filtered. The imine prepared above was added to the ether solution of diethyloxalacetate and the mixture stirred at room temperature for 4 days. The solvent was evaporated, the residue was triturated with ether and collected by filtration to give 41.2 g (78%) of the title compound (I-3a). ^{1}H NMR ($CDCl_3$): δ 1.16 (t, J = 7.1 Hz, 3H), 4.17 (m, 2H), 6.39 (s, 1H), 6.92 (dd, J = 7.6, 1.8 Hz, 1H), 7.11-7.27 (m, 4H), 7.35 (dd, J = 7.6, 1.4 Hz, 1H), 7.50 (m, 2H).

The following intermediates were prepared using procedures analogous to those described above for the synthesis of intermediate I-3a using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

ethyl 5-(2-chloro-4-fluorophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3b)

ethyl 5-(2,4-difluorophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3c)

ethyl 5-(3-fluorophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3d)

ethyl 5-(2,3-dichlorophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3e)

ethyl 5-(3-chlorophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3f)

ethyl 5-(4-chlorophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3g)

ethyl 5-(3-bromophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3h)

ethyl 5-(2-chlorophenyl)-1-(4-methoxyphenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3i)

ethyl 5-(2-chlorophenyl)-1-(4-bromophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3j)

ethyl 5-(3-fluorophenyl)-1-(4-bromophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3k)

ethyl 5-(3-bromophenyl)-1-(4-bromophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3l)

ethyl 5-(3-bromophenyl)-1-(4-fluorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3m)

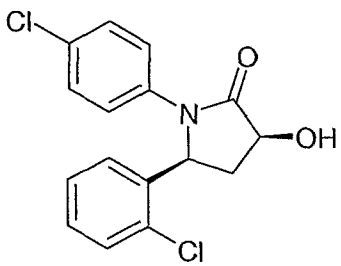
ethyl 5-(3-chlorophenyl)-1-(4-bromophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3n)

ethyl 5-(2-chlorophenyl)-1-(2-pyridyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3o)

ethyl 5-(3-bromophenyl)-1-(5-chloro-2-pyridyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3p)

ethyl 5-(3-chlorophenyl)-1-(4-cyanophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3q)

Preparation of Intermediate (3RS,5RS)-5-(2-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4a):



I-4a

A solution of 41.2 g (105 mmol) of ethyl 5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3a), 18.5 g (210 mmol) of sodium hypophophite hydrate and 100 ml of conc HCl in 300 ml of glacial acetic acid was refluxed for 18 h. The mixture

was cooled and concentrated *in vacuo*, the residue was taken up in water, made basic with conc ammonium hydroxide, and extracted with ethyl acetate (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. The crude product was triturated with minimal amounts of ether. The supernatant was evaporated and the residue triturated with ether. The combined solids gave 16.2 g (48%) of the title compound (I-4a) as a mixture of *cis* and *trans* isomers in an approximate 9:1 ratio. ^{1}H NMR ($CDCl_3$): δ 1.85 (bs, 1H), 2.17 (bs, 1H, OH), 3.05 (dt, J = 12.9, 7.8 Hz, 1H), 4.53 (t, J = 9.1 Hz, 1H), 5.62 (bs, 1H), 7.1-7.4 (m, 8H).

The following compounds were prepared using procedures analogous to those described above for the synthesis of Compound I-4a using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

(3RS,5RS)-5-(2,4-difluoro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4b)

(3RS,5RS)-5-(2-chloro-4-fluoro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4c)

(3RS,5RS)-5-(2-chloro-phenyl)-1-(4-methoxy-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4d)

(3RS,5RS)-5-(3-chloro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4e)

(3RS,5RS)-5-(3-fluoro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4f)

(3RS,5RS)-5-(3-bromo-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4g)

(3RS,5RS)-5-(3-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-3h)

(3RS,5RS)-5-(3-chloro-phenyl)-1-(3-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4i)

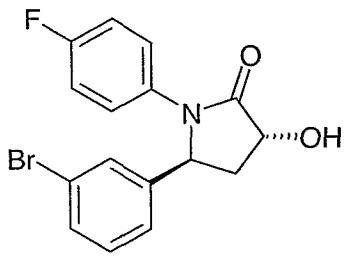
(3RS,5RS)-5-(3-bromo-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4j)

(3RS,5RS)-5-(2,3-dichloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4k)

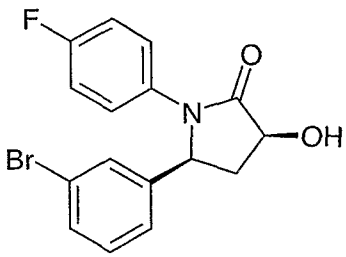
(3RS,5RS)-5-(2-chloro-4-fluoro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4l)

(3RS,5RS)-5-(3-chloro-phenyl)-1-(2-chloro-2-pyridyl)-3-hydroxy-pyrrolidin-2-one (I-4m)

Preparation of Intermediates (3SR,5RS)-5-(3-bromo-phenyl)-1-(4-fluoro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-5a) and (3RS,5RS)-5-(3-bromo-phenyl)-1-(4-fluoro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-5b):



I-5a



I-5b

A solution of 20.4 g (48.6 mmol) of ethyl 5-(3-bromophenyl)-1-(4-fluorphenyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-3m), 12.8 g (146 mmol) of sodium hypophosphite hydrate, 150 ml of glacial acetic acid and 200 ml of conc HCl in was refluxed for 18 hours. The mixture was cooled and concentrated *in vacuo*, the residue was taken up in water, made basic

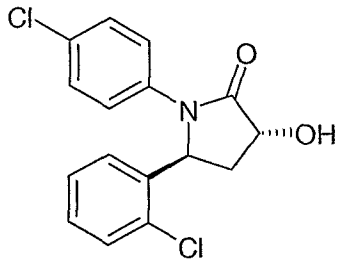
with concentrated ammonium hydroxide, and extracted with ethyl acetate (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification and separation of the cis and trans isomers was accomplished by silica gel MPLC using a 120 g Isco RediSep column eluting with 62% EtOAc / 38% hexane at 45 mL/minute. The trans *(3SR,5RS)* isomer (I-5a) eluted first giving 35 mg. ^{1}H NMR ($CDCl_3$): δ 2.45 (ddd, J = 12.9, 7.9, 2.5 Hz, 1H), 2.59 (dt, J = 12.9, 8.7 Hz, 1H), 4.67 (dd, J = 8.9, 8.1 Hz, 1H), 5.18 (dd, J = 8.7, 2.1 Hz, 1H), 6.98 (m, 2H), 7.07 (bd, J = 6.6, 1H), 7.20 (t, J = 7.7, 1H), 7.32 (t, J = 1.9 Hz, 1H), 7.42 (m, 3H).

The cis *(3RS,5RS)* isomer (I-5b) eluted second (19-33 min) giving 6.29 g (37%). ^{1}H NMR ($CDCl_3$): δ 2.01 (dt, J = 12.9, 9.1, 1H), 3.01 (ddd, J = 12.9, 8.3, 6.6 Hz, 1H), 3.70 (bs, 1H, OH), 4.60 (t, J = 8.9 Hz, 1H), 5.02 (dd, J = 8.7, 6.6 Hz, 1H), 6.95 (m, 2H), 7.13 (m, 2H), 7.26 (m, 2H), 7.36 (m, 2H).

The following compounds were prepared using procedures analogous to those described above for the synthesis of Compounds I-5a and I-5b using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

(3SR,5RS)-5-(2-chloro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-5c) and (3RS,5RS)-5-(2-chloro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-5d)

Preparation of Intermediate (3RS,5SR)-5-(2-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-6a):

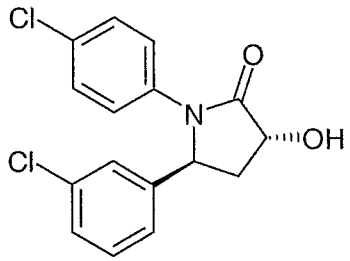


I-6a

A solution of 0.775 g (2.53 mmol) of 1-(4-chloro-phenyl)-5-(2-chloro-phenyl)-pyrrolidin-2-one (I-2a) in 15 ml of dry THF was chilled to -78 °C and treated with 2.5 ml (5.0 mmol) of LDA (2.0 M solution in THF) and allowed to stir for 30 minutes. A solution of 0.827 g (3.16 mmol) of 2-benzenesulfonyl-3-phenyl-oxaziridine (Lishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Syn.*, **1987**, *66*, 203-210) in 10 ml of THF was added dropwise. The mixture was kept at -78°C for 1 hour then allowed to warm to room temperature overnight. The reaction was quenched with satd ammonium chloride and extraced with ethyl acetate (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by silica gel MPLC with in chloroform with a gradient of methanol cosolvent from 1% to 3% gave 257 mg (32%) of the title compound (I-6a). MH+262. ^{1}H NMR ($CDCl_3$): δ 2.6 (m, 2H), 3.98 (s, 1H, OH), 4.57 (t, J = 9.1 Hz, 1H), 5.58 (dd, J = 1.7, 8.3 Hz, 1H), 6.98 (dd, J = 1.7, 7.5 Hz, 1H), 7.16 (dt, J = 0.8, 7.5 Hz, 1H),

7.3 (m, 3H), 7.44 (dd, J = 1.2, 7.8 Hz, 1H), 7.50 (m, 2H). HRMS calcd for $C_{16}H_{14}Cl_2NO_2$ (MH+): 322.0402, found: 322.0417.

Preparation of Intermediate (3SR,5RS)-5-(3-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-7a).



I-7a

Step A. A solution of 1.82 g (5.6 mmol) of (3RS,5RS)-5-(3-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4a), 2.07 g (16.9 mmol) of benzoic acid and 4.13 g (14.1 mmol) of triphenylphosphine in 85 mL THF was treated with 22 mL (11.3 mmol) of diisopropyl azodicarboxylate dissolved in 40 mL THF. The solution stirred at ambient temperature for 24 hours. The mixture was concentrated *in vacuo*, diluted with EtOAc, washed with water and brine, and the organic phase dried (sodium sulfate), filtered and evaporated. Purification by MPLC on a 100 g silica gel column eluting with solvent a gradient ranging from 10% EtOAc / 90% hexane to 30% EtOAc / 70% hexane gave 2.66 g of partially purified trans benzoate ester.

Step B. A solution of 2.6g (6 mmol) of the trans benzoate ester from Step A in 60 mL of methanol and treated with a solution of 3.55 g (62 mmol) of potassium hydroxide in 60 mL of 50/50 methanol/water. After 2 hours at room temperature, the reaction mixture was concentrated *in vacuo*, diluted with water and extracted with EtOAc (3x). The combined organic layers were dried (sodium sulfate), filtered and evaporated. Purifcation by MPLC on a 120 g silica gel column eluting with a solvent gradient of 30% EtOAc / 70% hexane to 40% EtOAc / 60% hexane over 30 minutes and a second gradient from 40% EtOAc / 60% hexane to 20% EtOAc / 80% hexane over 20 min gave 1.74 g (97%) of the title compound (I-7a).

^{1}H NMR ($CDCl_3$): δ 2.48 (ddd, J = 12.4, 7.9, 2.1 Hz, 1H), 2.56 (ddd, J = 12.4, 9.1, 8.2 Hz, 1H), 2.87 (2.87, bt, 1H), 4.60 (ddd, J = 10.0, 8.3, 2.1 Hz, 1H), 5.21 (dd, J = 8.5, 1.9 Hz, 1H), 7.03 (m, 1H), 7.16 (m 1H), 7.25-7.29 (m, 4H), 7.48 (m, 2H). MS 427 (M+H).

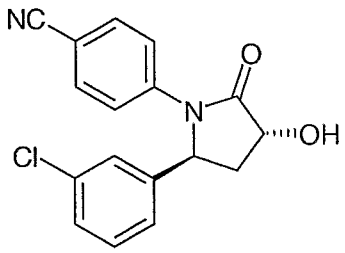
The following compounds were prepared using procedures analogous to those described above for the synthesis of Compound I-7a using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

(3SR,5RS)-5-(2,3-dichloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-7b)

(3SR,5RS)-5-(2-chloro-4-fluoro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-7c)

(3SR,5RS)-5-(4-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-7d)

Preparation of Intermediate (3SR,5RS)-5-(3-chloro-phenyl)-1-(4-cyano-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8a).



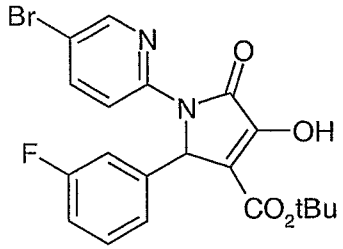
I-8a

A mixture of 1.58 g (4.1 mmol) of (3SR,5RS)-5-(3-chloro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4e), 0.48 g (4.1 mmol) of zinc cyanide and 0.95 g (0.8 mmol) of palladium tetrakis(triphenylphosphine) in 24 mL DMF was heated at 85 °C for 4 hours (Tschaen, DM. *et al. Synth. Commun.*, **1994**, *24*, 887-890). The reaction was cooled to room temperature, poured into 200 mL EtOAc and washed with water (2x). The organic layer was dried (magnesium sulfate), filtered and evaporated. Purification by MPLC on a 120g silica gel column eluting with a solvent gradient from 25% EtOAc / 75% hexane to 50% EtOAc / 50% hexane at 45 mL/min gave 1.06 g (83%) of the title compound (I-8a). ^{1}H NMR ($CDCl_3$): δ 2.50 (ddd, J = 12.4, 7.9, 2.1 Hz, 1H), 2.60 (ddd, J = 12.4, 9.5, 8.3 Hz, 1H), 3.70 (d, J = 2.5 Hz, 1H), 4.64 (ddd, J = 10.4, 7.9, 2.5 Hz, 1H), 5.27 (dd, J = 8.7, 2.1 Hz, 1H), 7.02 (m, 1H), 7.15 (m, 1H), 7.29 (m, 2H), 7.57 (dt, J = 9.1, 2.3 Hz, 2H), 7.70 (dt, J = 9.1, 2.3 Hz, 2H).

The following compounds were prepared using procedures analogous to those described above for the synthesis of Compound I-8a using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

(3RS,5RS)-5-(3-cyano-phenyl)-1-(4-cyano-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8b)
(3RS,5RS)-5-(3-chloro-phenyl)-1-(3-cyano-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8c)
(3SR,5RS)-5-(3-cyano-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8d)
(3S,5R)-5-(2-chloro-phenyl)-1-(4-cyano-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8e)
(3S,5R)-5-(3-fluoro-phenyl)-1-(4-cyano-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8f)
(3R,5S)-5-(3-fluoro-phenyl)-1-(4-cyano-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8g)
(3SR,5RS)-5-(3-cyano-phenyl)-1-(4-fluoro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8h)
(3RS,5RS)-5-(3-cyano-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-8i)

Preparation of Intermediate t-butyl 5-(3-fluorophenyl)-1-(5-bromo-2-pyridyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-9a):



I-9a

A mixture of 3.00 g (17.3 mmol) of 2-amino-5-bromopyridine and 2.15 g (17.3 mmol) of 3-fluorobenzaldehyde in 75 mL of toluene was heated at reflux with a Dean-Stark trap for 3 days. The solution was cooled to room temperature and 5.46 g (22.5 mmol) of di-t-butyl oxalacetate (Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.*, **1983**, *48*, 5017-5022) was added. The solution was heated at 45-50 °C for 48 hours. The solution was cooled to room temperature and the solvent removed under reduced pressure. The solid residue was triturated with ethyl ether, then collected by filtration, washed with ethyl ether and dried *in vacuo* to give 4.71 g (60.5%) of the title compound (I-9a). ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 9H), 6.08 (s, 1H), 7.1-7.3 (m, 4H), 7.32 (s, 1H), 7.63 (dd, J = 2.5, 9.1 Hz, 1H), 8.16 (d, J = 2.5 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H). M+ 449.

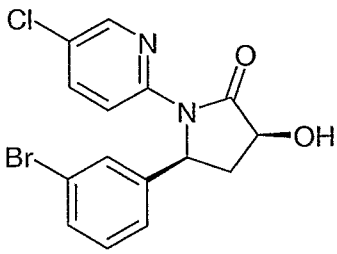
The following compounds were prepared using procedures analogous to those described above for the synthesis of Compound I-9a using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

5-(3-chlorophenyl)-1-(5-chloro-2-pyridyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-9b)

5-(3-bromophenyl)-1-(5-chloro-2-pyridyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-9c)

5-(3-cyanophenyl)-1-(5-chloro-2-pyridyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (I-9d)

Preparation of Intermediate (3RS,5RS)-5-(3-bromo-phenyl)-1-(5-chloro-2-pyridyl)-3-hydroxy-pyrrolidin-2-one (I-10a).



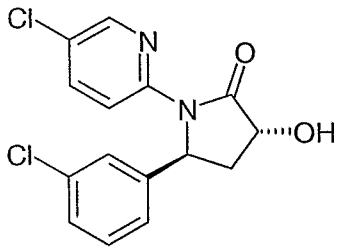
I-10a

Step A. A solution of 214 mg (0.46 mmol) of 5-(3-bromophenyl)-1-(5-chloro-2-pyridyl)-3-hydroxy-2-oxo-2,5-dihydro-1H-pyrrole-4-carboxylate (compound I-9c) in 2 mL of trifluoroacetic acid was heated at reflux for 16 hours. The solution was cooled to room temperature and

concentrated *in vacuo* to give 5-(3-bromo-phenyl)-1-(5-chloro-2-pyridyl)-pyrrolidin-2,3-dione which was used without purification in the next step.

Step B. A solution of 5-(3-bromo-phenyl)-1-(5-chloro-2-pyridyl)-pyrrolidin-2,3-dione from Step A (theoretical 186 mg, 0.46 mmol) in 3 mL methanol was treated with 60 mg (1.6 mmol) of sodium borohydride at room temperature for 16 hours. The mixture was diluted with ethyl acetate, washed with water and brine, and the organic layer was dried (sodium sulfate), filtered and evaporated. Purification by MPLC on a 40 g silica gel colum eluting at 30 mL/minute (solvent program: 30% EtOAc / 70% hexane for 20 minutes, ramp to 50% EtOAc / 50% hexane over 20 minutes) gave 126 mg (75%) of the title compound (I-10a). ^{1}H NMR ($CDCl_3$): δ 1.97 (dt, J = 13.3, 8.7Hz, 1H), 2.98 (ddd, J = 15.8, 8.7, 7.2 Hz, 1H), 4.59 (t, J = 8.9 Hz, 1H), 5.44 (t, J = 7.9 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 1.17 (dt, J = 7.5, 1.5, 1H), 7.32 (dt, J = 7.5, 1.5 Hz, 1H), (dd, J = 9.1, 2.5 Hz, 1H), 8.10 (m, 2H).

Preparation of Intermediate (3RS,5SR)-5-(3-chloro-phenyl)-1-(5-chloro-2-pyridyl)-3-hydroxy-pyrrolidin-2-one (I-11a).



I-11a

Step A. A solution in 10 mL THF was prepared with 0.38 g (1.2 mmol) of (3RS,5RS)-5-(3-chloro-phenyl)-1-(5-chloro-2-pyridyl)-3-hydroxy-pyrrolidin-2-one (I-4m), 0.78 g (2.9 mmol) of N-Boc-L-phenylalanine and 0.77 g (0.29 mmol) of triphenylphospine. A solution of 0.46 mL (1.03 mmol) of diisopropyl azodiacarboxylate in 10 mL THF was added over 30 minutes. The solution stirred at ambient temperature for 16 hours, then partitioned with water and EtOAc. The layers were separated and the aqueous phase extracted with EtOAc (2x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by MPLC eluting with 20% EtOAc : 80% hexane at 45 mL/minute on a 120 g silica gel column gave 0.49 g (73%) as a mixture of diastereomers (i.e. the trans N-Boc-Phe esters).

Step B. The mixture of diastereomers from Step A was dissolved in 7 mL methanol and treated with a solution of 51 mg (2.1 mmol) of lithium hydroxide in 7 mL of 50/50 methanol/water. The solution stirred at ambient temperature for 5 minutes, concentrated *in vacuo*, diluted with water and extracted with EtOAc (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by MPLC on a 40 g silica gel column eluting with 40% EtOAc : 60% hexane at 24 mL/minute gave 0.23 g (83%) of the title compound (I-11a). ^{1}H NMR ($CDCl_3$): δ 2.53 (m, 2H), 3.48 (bs, 1H), 4.69 (dt, J = 1.9, 9.3 Hz, 1H), 5.82 (t, J = 5.0 Hz),

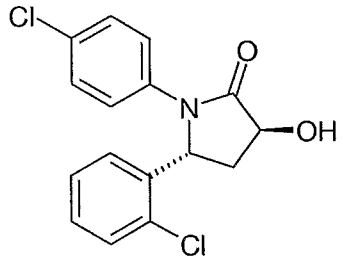
7.00 (m, 1H), 7.12 (m, 1H), 7.21 (m, 2H), 7.67 (dd, J = 8.9, 2.7), 8.15 (dd, J = 2.9, 0.8), 8.46 (m, 2H).

The following compounds were prepared using procedures analogous to those described above for the synthesis of Compound I-11a using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

(3RS,5SR)-5-(3-fluoro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-11b)

(3RS,5SR)-5-(3-bromo-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-11c)

Preparation of Intermediate (3S,5R)-5-(2-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12a).



I-12a

Step A. A solution of 10.0 g (31 mmol) of (3RS,5RS)-5-(2-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (compound I-4a), 24.7 g (93.1 mmol) of N-Boc-L-phenylalanine and 20.3 g (77.5 mmol) of triphenyl phosphine was prepared in 300 mL THF. A solution of 12.2 mL (62 mmol) of diisopropyl azodicarboxylate in 200 mL THF was added over 30 minutes and the solution stirred at ambient temperature for 48 hours. The solution was diluted with EtOAc, washed with brine (2x), dried (magnesium sulfate), filtered and evaporated. Purification by MPLC on a 120 g silica gel column eluting at 39 mL/minute with 10% EtOAc : 90% hexane for 33 minutes and ramping to 18% EtOAc : 82% hexane over 33 min. The isomer eluting first was isolated to give 4.61 g (26%) of the (3S,5R)-N-Boc-Phe ester.

Step B. A solution of 4.61 g (8.09 mmol) of the (3S,5R)-N-Boc-Phe ester from Step A in 100 mL of methanol was mixed with a solution of 4.54 g (80.9 mmol) of potassium hydroxide in 50/50 methanol/water. The solution stirred at ambient temperature for 30 minutes, then was concentrated *in vacuo*, diluted with water and extracted with EtOAc (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by MPLC on a 120 g silica gel column eluting at 36 mL/minute with 90% EtOAc : 10% hexane gave 2.3 g (88%) of the title compound (I-12a). ^{1}H NMR ($CDCl_3$): δ 2.56 (m, 2H), 3.77 (d, J = 2.9 Hz, 1H), 4.57 (ddd, J = 10.0, 8.3, 2.9 Hz, 1H), 5.59 (dd, J = 7.5, 1.7 Hz, 1H), 7.16 (dt, J = 1.2, 7.5 Hz, 1H), 7.25 (m, 3H), 7.45 (dd, J = 7.9, 1.2 Hz, 1H), 7.49 (m, 2H).

The following compounds were prepared using procedures analogous to those described above for the synthesis of Compound I-12a using the appropriate starting materials which are

available commercially or prepared using preparations well-known to those skilled in the art. For the 5-(2-substituted)phenyl derivatives separated in Step A, the (3S,5R) diastereomer generally elutes first. For the 5-(3-substituted)phenyl derivates separated in Step A, the (3R,5S) diastereomer generally elutes first.

(3S,5R)-5-(3-cyano-phenyl)-1-(4-cyano-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12b)
Chiral auxiliary: (1S)-(-)-camphanic acid
Hydrolysis: LiOH / MeOH / water

(3S,5R)-5-(2-chloro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12c)
Chiral auxiliary: N-Boc-phenylalanine
Hydrolysis: KOH / MeOH / water

(3S,5R)-5-(3-fluoro-phenyl)-1-(4-bromo-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12d)
Chiral auxiliary: N-Boc-alanine
Hydrolysis: KOH / MeOH / water

(3S,5R)-5-(3-bromo-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12e)
Chiral auxiliary: N-Boc-alanine
Hydrolysis: LiOH / MeOH / water

(3S,5R)-5-(3-chloro-phenyl)-1-(5-chloro-pyridin-2-yl)-3-hydroxy-pyrrolidin-2-one (I-12f)
Chiral auxiliary: (1S)-(-)-camphanic acid
Hydrolysis: LiOH / MeOH / water

(3S,5R)-5-(2-chloro-phenyl)-1-(4-methoxy-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12g)
Chiral auxiliary: N-Boc-phenylalanine
Hydrolysis: KOH / MeOH / water

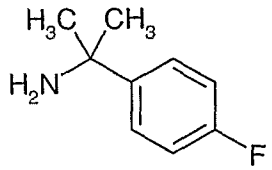
(3R,5S)-5-(2-chloro-phenyl)-1-(4-methoxy-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12h)
Chiral auxiliary: N-Boc-phenylalanine
Hydrolysis: KOH / MeOH / water

(3S,5R)-5-(3-bromo-phenyl)-1-(5-chloro-pyridin-2-yl)-3-hydroxy-pyrrolidin-2-one (I-12i)
Chiral auxiliary: (1S)-(-)-camphanic acid
Hydrolysis: LiOH / MeOH / water

(3S,5R)-5-(3-cyano-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12j)
Chiral auxiliary: N-Boc-phenylalanine
Hydrolysis: LiOH / MeOH / water

(3R,5S)-5-(3-cyano-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-12k)
Chiral auxiliary: N-Boc-phenylalanine
Hydrolysis: LiOH / MeOH / water

Preparation of intermediate 1-(4-fluorophenyl)-1-methyl-ethylamine (I-13a).



I-13a

Step A. Anhydrous cerium (III) chloride was prepared by placing 55.38 g of cerium (III) chloride heptahydrate in a round bottom flask equipped with stir bar and vacuum adapter. The flask was heated slowly to 160°C over 2-3 hours under 0.5 mm vacuum and held at that temperature and pressure for 12h. The flask was cooled to ambient temperature under vacuum and used immediately in the next step.

Step B. The anhydrous cerium (III) chloride from Step A (theoretical 36.63 g, 0.149 mol) was chilled to 0°C and 100 mL of cold THF was added. The mixture was cooled to -78°C and treated dropwise with 99.1 mL (0.149 mol) of 1:1 methyllithium / lithium bromide complex (1.5 M in ethyl ether). The mixture was stirred for 45 minutes at –78°C. A solution of 6.00 g (49.54 mmol) of 4-fluorobenzonitrile in 50 mL dry THF was added dropwise, and after stirring for another 40 minutes at –78°C, the mixture was allowed to warm to ambient temperature. The reaction was quenched with 90 mL of aqueous ammonium hydroxide and allowed to stir 12 hours. The mixture was filtered through celite and the filtrate evaporated. The residue was dissolved in diethyl ether, dried (magnesium sulfate), filtered and evaporated. Purification by MPLC with a solvent gradient from 0% MeOH : 100% $CHCl_3$ to 6% MeOH : 94% $CHCl_3$ gave 7.07 g (93.0%) of the title compound. ^1H NMR ($CDCl_3$): δ 1.48 (s, J = 6.69, 6H), 7.00 (m, 2H), 7.46 (m, 2H).

The following compounds were prepared using procedures analogous to those described above for the synthesis of Compound I-13a using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

1-(3-trifluoromethyl-phenyl)-1-methyl-ethylamine (I-13b)

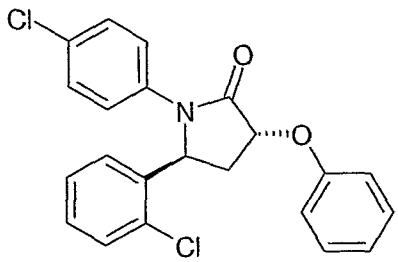
1-[3-(1-amino-1-methylethyl)phenyl]pyrrolidin-2-one (I-13c)

2-[3-(1-amino-1-methylethyl)phenyl]propan-2-ol (I-13d)

2-[4-(1-amino-1-methylethyl)phenyl]propan-2-ol (I-13e)

Example 1

Preparation of (3RS,5SR)-5-(2-chloro-phenyl)-1-(4-chloro-phenyl)-3-phenoxy-pyrrolidin-2-one (1.01):

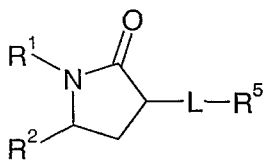


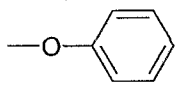
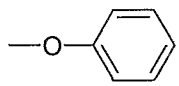
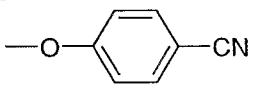
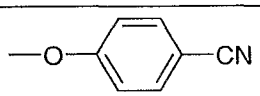
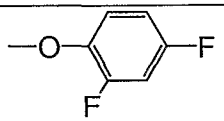
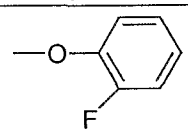
1.01

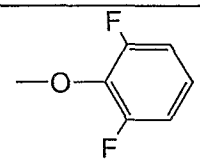
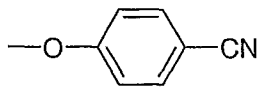
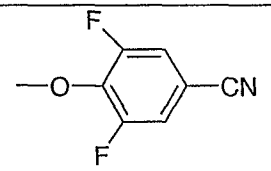
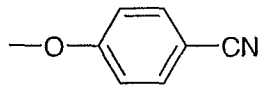
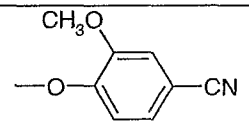
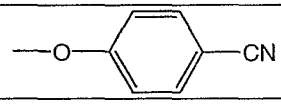
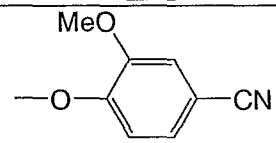
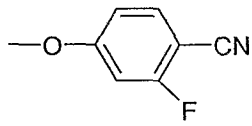
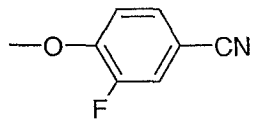
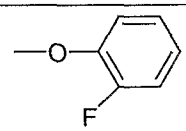
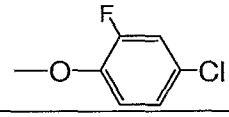
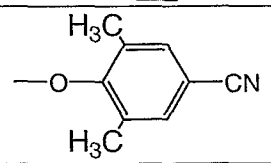
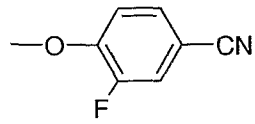
A solution of 0.20 g (0.62 mmol) of (3RS,5RS)-5-(2-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-4a) in 10 mL of dry THF under nitrogen atmosphere was treated with 0.407 g (1.55 mmol) of triphenyl phosphine and 0.292 g (3.10 mmol) phenol. A solution of 1.03 mL (1.24 mmol) of diisopropyl azodicarboxylate in 5 mL of dry THF was added over 30 min, and the mixture stirred at ambient temperature for 16 hours. The mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by MPLC with a solvent gradient from 4% EtOAc: 96% hexane to 9% EtOAc: 91% hexane gave 0.106 g (43%) of the title compound (1.01). ^{1}H NMR ($CDCl_3$): 2.62 (ddd, J = 13, 7.6, 2.5 Hz, 1H), 2.78 (dt, J = 13.3, 8.5 Hz, 1H), 5.08 (t, J = 8.1 Hz, 1H), 5.70 (dd, J = 8.5, 2.3 Hz, 1H), 7.03 (m, 4H), 7.25 (m, 6H), 7.46 (dd, J = 7.7, 1.4 Hz, 1H), 7.53 (m, 2H).

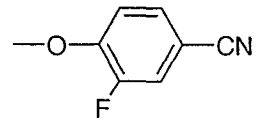
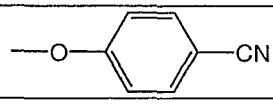
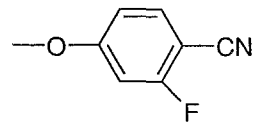
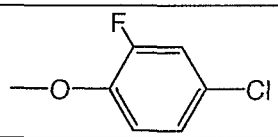
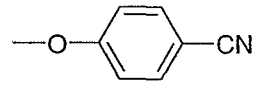
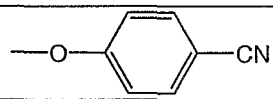
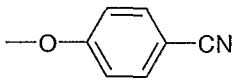
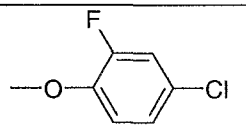
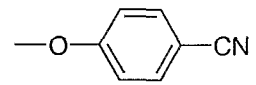
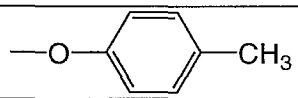
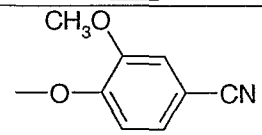
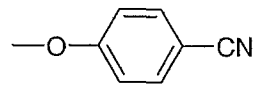
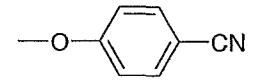
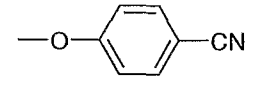
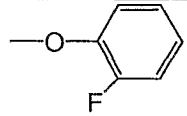
The following compounds listed in Table 1 were prepared using procedures analogous to those described above for the synthesis of Compound 1.01 using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

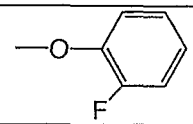
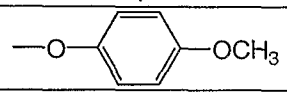
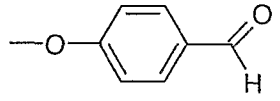
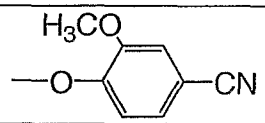
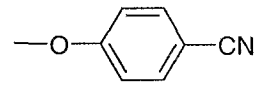
Table 1



Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
1.01[4h]	3RS,5RS	4-chloro-phenyl	2-chloro-phenyl		398
1.02[5h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		398
1.03[2h]	3RS,5RS	4-chloro-phenyl	2-chloro-phenyl		423
1.04[4h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		423
1.05[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		434
1.06[2h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		416

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
1.07[4h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		434
1.08[5h]	3RS,5SR	4-chloro-phenyl	2-chloro-4-fluoro-phenyl		441
1.09[4h]	3RS,5SR	4-chloro-phenyl	2-chloro-4-fluoro-phenyl		477
1.10[6h]	3RS,5SR	6-chloro-pyridin-3-yl	2-chloro-phenyl		424
1.11[5h]	3RS,5SR	6-chloro-pyridin-3-yl	2-chloro-phenyl		454
1.12[5h]	3RS,5SR	4-chloro-phenyl	2,4-difluoro-phenyl		425
1.13[8h]	3RS,5SR	pyridin-3-yl	2-chloro-phenyl		420
1.14[5h]	3RS,5SR	4-chloro-phenyl	2,4-difluoro-phenyl		443
1.15[6h]	3RS,5SR	4-chloro-phenyl	2,4-difluoro-phenyl		443
1.16[8h]	3RS,5SR	pyridin-3-yl	2-chloro-phenyl		383
1.17[8h]	3RS,5SR	pyridin-3-yl	2-chloro-phenyl		417
1.18[8h]	3RS,5SR	4-chloro-phenyl	2-chloro-4-fluoro-phenyl		469
1.19[6h]	3RS,5SR	4-chloro-phenyl	2-chloro-4-fluoro-phenyl		459

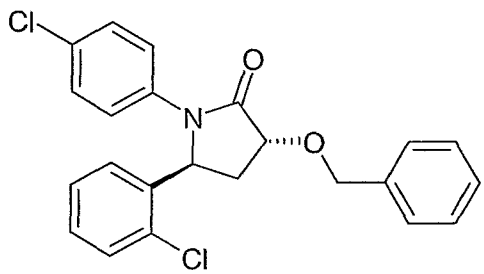
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
1.20[5h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		441
1.21[4h]	3RS,5RS	6-chloro-pyridin-3-yl	2-chloro-phenyl		424
1.22[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		441
1.23[6h]	3RS,5SR	6-chloro-pyridin-3-yl	2-chloro-phenyl		451
1.24[7h]	3RS,5SR	pyridin-3-yl	2-chloro-phenyl		390
1.25[4h]	3RS,5SR	5-chloro-pyridin-2-yl	2-chloro-phenyl		424
1.26[6h]	3RS,5SR	5-methyl-pyridin-2-yl	2-chloro-phenyl		404
1.27[4h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		450
1.28[2h]	3RS,5SR	4-methoxy-phenyl	2-chloro-phenyl		419
1.29[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		412
1.30[4h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		453
1.31[6h]	3RS,5SR	4-dimethyl-amino-phenyl	2-chloro-phenyl		432
1.32[3h]	3S,5S	4-methoxy-phenyl	2-chloro-phenyl		419
1.33[3h]	3R,5R	4-methoxy-phenyl	2-chloro-phenyl		419
1.34[5h]	3S,5S	4-methoxy-phenyl	2-chloro-phenyl		412

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
1.35[5h]	3R,4R	4-methoxy-phenyl	2-chloro-phenyl		412
1.36[5h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		428
1.37[4h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		426
1.38[5h]	3RS,5SR	5-chloro-pyridin-2-yl	2-chloro-phenyl		454
1.39[5h]	3RS,5SR	phenyl	2-chloro-phenyl		389

[1h]human CB-1 binding Ki is < 1 nM
[2h]human CB-1 binding Ki is < 10 nM
[3h]human CB-1 binding Ki is < 50 nM
[4h]human CB-1 binding Ki is <100 nM
[5h]human CB-1 binding Ki is < 250 nM
[6h]human CB-1 binding Ki is < 500 nM
[7h]human CB-1 binding Ki is <1000 nM
[8h]human CB-1 binding Ki is ≤ 4000 nM

Example 2

Preparation of (3RS,5SR)-3-(benzyloxy)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-pyrrolidin-2-one (2.01):



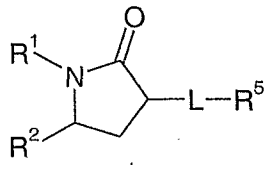
2.01

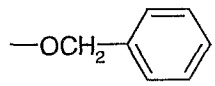
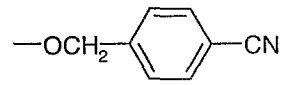
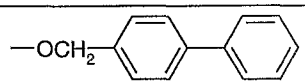
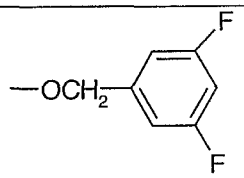
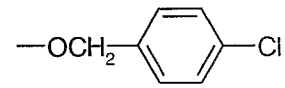
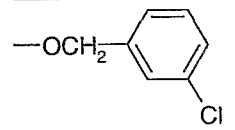
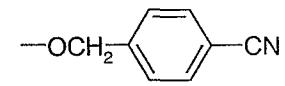
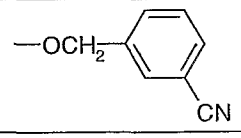
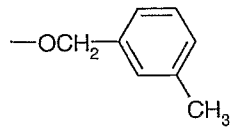
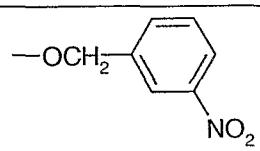
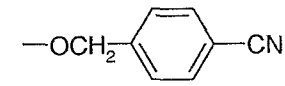
A solution of 0.19 g (0.59 mmol) of (3RS,5SR)-5-(2-chloro-phenyl)-1-(4-chloro-phenyl)-3-hydroxy-pyrrolidin-2-one (I-6a) in 10 mL dry THF under nitrogen atmosphere was treated with 0.047 g (1.19 mmol) of NaH over 30 minutes. A solution of 0.11 mL benzyl bromide in 5 mL dry THF was added dropwise and the mixture stirred at ambient temperature for 2 hours. The mixture was quenched slowly with NH_4Cl, diluted with water, and extracted ethyl acetate (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by MPLC with 8% EtOAc: 92% hexane gave .046 g (19%) of the title compound (2.01). ^1H NMR ($CDCl_3$): 2.39 (ddd, J = 13.3, 7.9, 2.9 Hz, 1H), 2.65 (dt, J = 13.3, 8.3 Hz, 1H), 4.34 (t, J = 8.1 Hz, 1H), 4.78 (d, J = 12.0 Hz, 1H), 5.06 (d, 1H), 5.65 (dd, J = 8.5, 2.7 Hz, 1H), 6.98 (dd, J = 7.5, 1.7 Hz, 1H), 7.16 (dt, 7.5, 1.2 Hz, 1H), 7.20-7.45 (m, 9H), 7.48 (m, 2H).

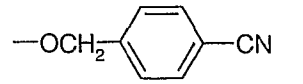
The following compounds listed in Table 2 were prepared using procedures analogous to those described above for the synthesis of Compound 2.01 using the appropriate starting

materials which are available commercially or prepared using preparations well-known to those skilled in the art.

Table 2



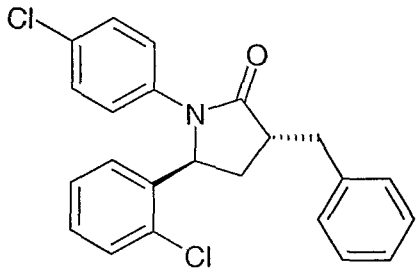
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
2.01[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		412
2.02[2h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		437
2.03[4h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		488
2.04[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		448
2.05[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		446
2.06[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		446
2.07[4h]	3RS,5RS	4-chloro-phenyl	2-chloro-phenyl		437
2.08[8h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		437
2.09[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		426
2.10[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		457
2.11[2h]	3RS,5RS	4-chloro-phenyl	2-chloro-4-fluoro-phenyl		455

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
2.12[8h]	3RS,5RS	pyridin-3-yl	2-chloro-phenyl		404

[1h]human CB-1 binding Ki is < 1 nM
[2h]human CB-1 binding Ki is < 10 nM
[3h]human CB-1 binding Ki is < 50 nM
[4h]human CB-1 binding Ki is <100 nM
[5h]human CB-1 binding Ki is < 250 nM
[6h]human CB-1 binding Ki is < 500 nM
[7h]human CB-1 binding Ki is <1000 nM
[8h]human CB-1 binding Ki is ≤ 4000 nM

Example 3

Preparation of (3RS,5SR)-3-benzyl-5-(2-chlorophenyl)-1-(4-chlorophenyl)pyrrolidin-2-one (3.01):

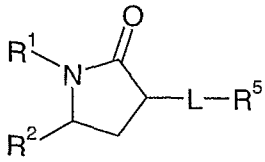


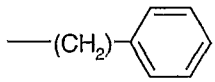
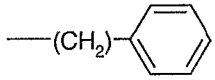
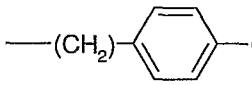
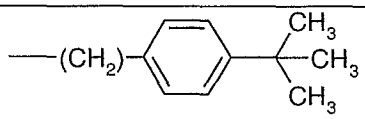
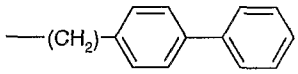
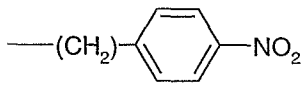
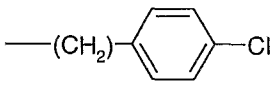
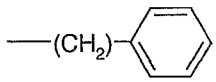
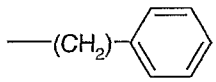
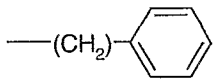
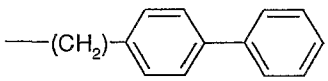
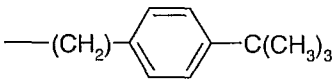
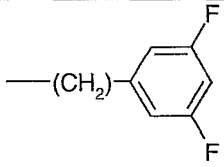
3.01

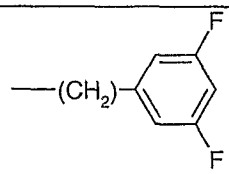
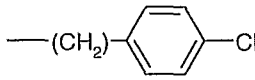
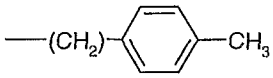
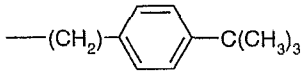
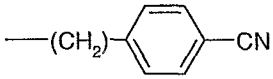
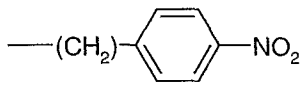
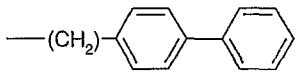
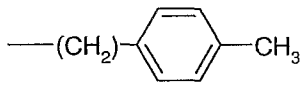
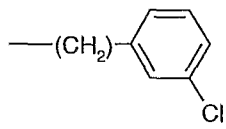
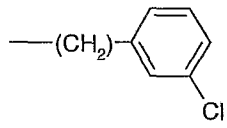
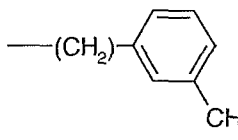
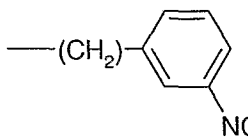
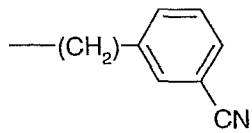
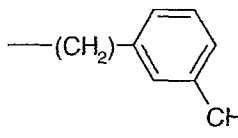
A solution of 0.23 mL (1.63 mmol) of diisopropylamine in 10 mL dry THF under nitrogen atmosphere was cooled to –78 °C and treated with n-BuLi. After 1 min. 0.25 g (0.82 mmol) of 1-(4-chloro-phenyl)-5-(2-chloro-phenyl)-pyrrolidin-2-one (I-2a) in 5 mL of dry THF at –78 °C was added to the mixture and stirred for 40 minutes at –78 °C. The mixture was allowed to warm to ambient temperature over 12 hours, quenched with satd NH_4Cl, and extracted with EtOAc (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by MPLC with 20% EtOAc : 80% hexane gave 0.224 g (69.5%) of the title compound (3.01). ^1H NMR ($CDCl_3$): 2.05 (ddd, J = 12.9, 8.3, 2.1Hz, 1H), 2.38 (ddd, J = 12.9, 10.2, 8.5 Hz, 1H), 2.83 (dd, J = 13.7, 9.1 Hz, 1H), 2.96 (m, 1H), 5.37 (dd, J = 8.3, 2.1 Hz, 1H), 7.00 (dd, J = 7.7, 1.9 Hz, 1H), 7.1-7.3 (m, 9H), 7.37 (dd, J = 7.9, 1.7 Hz, 1H), 7.44 (m, 2H).

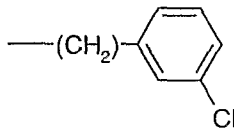
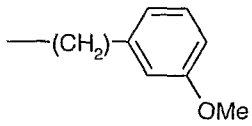
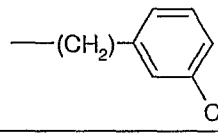
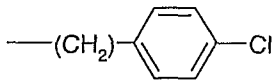
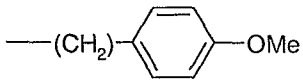
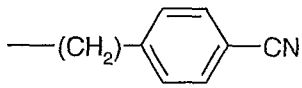
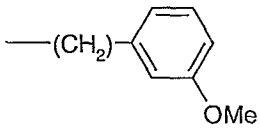
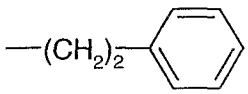
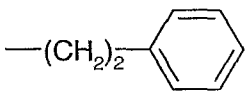
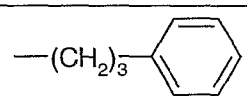
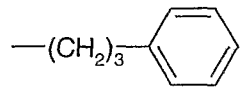
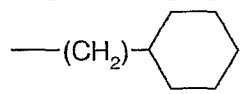
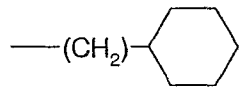
The following compounds listed in Table 3 were prepared using procedures analogous to those described above for the synthesis of Compound 3.01 using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art. Although the trans isomer is generally the major product from the method described for the preparation of Example 3.01, in some cases it is possible to isolate the cis isomer. Mixtures of cis and trans isomers may also be prepared according to the method described for Example 9. Separation of cis and trans isomers may be accomplished by methods known to those skilled in the art.

Table 3



Ex. No.	Stereo Chem	R^1	R^2	L-R^5	MS (M+H)
3.01[3r]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		396
3.02[2r]	3RS,5SR	4-chloro-phenyl	phenyl		362
3.03[2r]	3RS,5SR	4-chloro-phenyl	phenyl		387
3.04[4r]	3RS,5SR	4-chloro-phenyl	phenyl		418
3.05[5r]	3RS,5SR	4-chloro-p-henyl	phenyl		438
3.06[2h]	3RS,5SR	4-chloro-phenyl	phenyl		407
3.07[2h]	3RS,5SR	4-chloro-phenyl	phenyl		396
3.08[6r]	3RS,5SR	2-chloro-phenyl	4-chloro-phenyl		396
3.09[7r]	3RS,5SR	2-chloro-phenyl	2-chloro-phenyl		396
3.10[5r]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		396
3.11[5r]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		472
3.12[5r]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		452
3.13[4r]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		432

Ex. No.	Stereo Chem	R^1	R^2	L-R^5	MS (M+H)
3.14[2h]	3RS,5RS	4-chloro-phenyl	4-chloro-phenyl		432
3.15[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		430
3.16[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		410
3.17[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		452
3.18[2h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		421
3.19[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		441
3.20[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		472
3.21[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		410
3.22[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		430
3.23[2h]	3RS,5RS	4-chloro-phenyl	4-chloro-phenyl		430
3.24[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		410
3.25[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		441
3.26[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		421
3.27[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		410

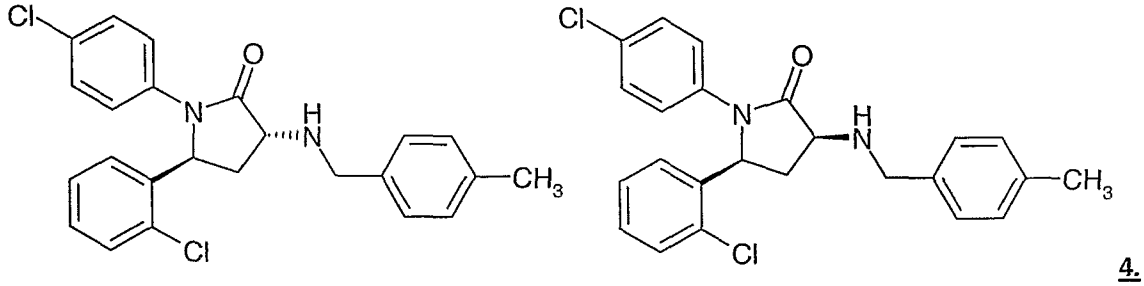
Ex. No.	Stereo Chem	R^1	R^2	L-R^5	MS (M+H)
3.28[2h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		421
3.29[3h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		426
3.30[2h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		430
3.31[2h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		430
3.32[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		426
3.33[2h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		421
3.34[3h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		426
3.35[4h]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		410
3.36[2r]	3RS,5SR	4-chloro-phenyl	phenyl		376
3.37[5h]	3RS,5SR	4-chloro-phenyl	4-chloro-phenyl		424
3.38[3h]	3RS,5SR	4-chloro-phenyl	Ph-enyl		390
3.39[3r]	3RS,5SR	4-chloro-phenyl	2-chloro-phenyl		402
3.40[3h]	3RS,5RS	4-chloro-phenyl	2-chlorophenyl		402

[1h]human. [1r]rat CB-1 binding Ki is < 1 nM
[2h]human, [2r]rat CB-1 binding Ki is < 10 nM
[3h]human, [3r]rat CB-1 binding Ki is < 50 nM
[4h]human, [4r]rat CB-1 binding Ki is <100 nM
[5h]human, [5r]rat CB-1 binding Ki is < 250 nM
[6h]human, [6r]rat CB-1 binding Ki is < 500 nM
[7h]human, [7r]rat CB-1 binding Ki is <1000 nM
[8h]human, [8r]rat CB-1 binding Ki is ≤ 4000 nM

5

Example 4

Preparation of (3RS,5SR)- and (3RS,5RS)-5-(2-chlorophenyl)-1-(4-chlorophenyl) -3-((4-methyl)phenylmethylamino)pyrrolidin-2-one (4.001 and 4.002):



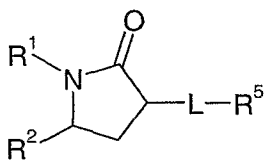
4.001 4.002

Step A. A solution of 4.73 g (14.7 mmol) of (3RS,5RS)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-hydroxypyrrolidin-2-one (I-4a) in 75 mL of dry methylene chloride was treated with 1.23 g (15.9 mmol) of pyridine. The solution was then treated dropwise with 4.35 g (15.4 mmol) of triflic anhydride at 0°C and allowed to return to ambient temperature. The solution was evaporated, triturated with ether, filtered through celite and the filtrate was evaporated. Purification by MPLC with 25% EtOAc : 75% hexane at 30 mL/min, 12 mL/tube provided 3.49 g (52%) of the triflate.

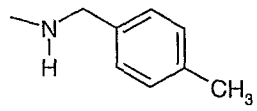
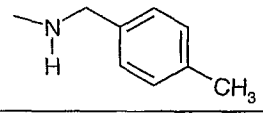
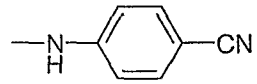
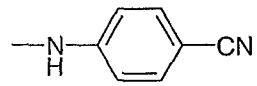
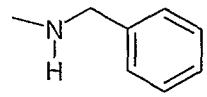
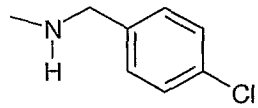
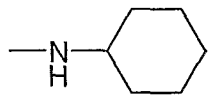
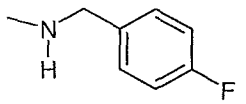
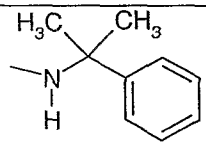
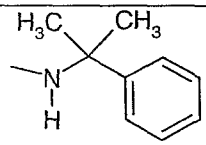
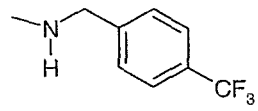
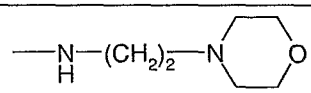
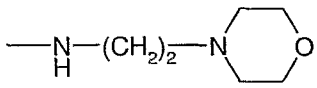
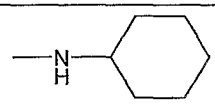
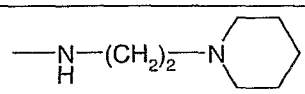
Step B. A solution of 0.20 g (0.44 mmol) of the triflate from Step A in 3 mL of dry methylene chloride was treated with 0.107 g (0.88 mmol) of 4-methyl benzyl amine and the mixture stirred at ambient temperature for 16 hours. Purification by MPLC with a solvent gradient from 7% EtOAc : 93% hexane to 15% EtOAc : 85% hexane for 13 minutes at 24 mL/minute gave 52 mg (28%) of the trans isomer and 23 mg (12%) of the cis isomer. Example 4.001 (trans isomer) - ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H), 2.38 (ddd, J = 12.6, 8.0, 1.7 Hz, 1H), 2.48 (ddd, J = 12.5, 10.0, 8.7 Hz, 1H), 3.71 (dd, J = 10.0, 7.9 Hz, 1H), 3.80 (d, J = 13 Hz, 1H), 3.84 (d, J = 13 Hz, 1H), 5.58 (dd, J = 8.7, 1.2 Hz, 1H), 6.99 (dd, J = 7.9, 1.7 Hz, 1H), 7.12-7.26 (m, 8H), 7.44 (dd, J = 7.9, 1.2 Hz, 1H), 7.50 (dt, J = 9.1, 2.3 Hz, 2H). Example 4.002 (cis isomer) - ^{1}H NMR ($CDCl_3$) (cis isomer): δ2.33 (s, 3H), 2.94 (m, 1H), 3.70 (dd, J = 10.0, 8.3 Hz, 1H), 3.83 (d, J = 13 Hz, 1H), 3.92 (d, J = 13 Hz, 1H), 5.63 (m, 1H), 7.1-7.3 (m, 12H).

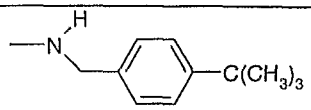
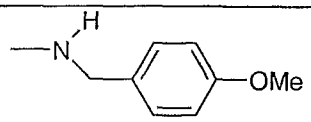
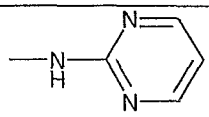
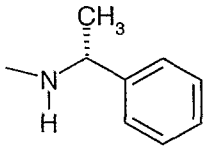
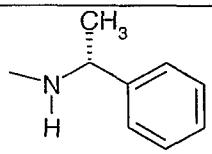
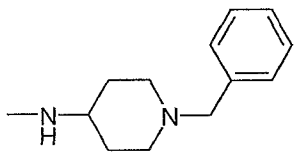
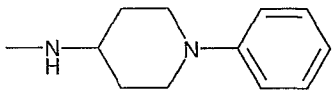
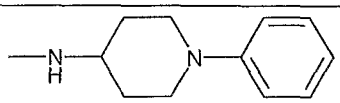
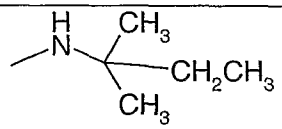
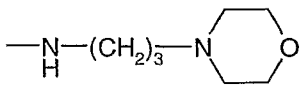
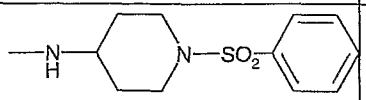
The following compounds listed in Table 4 were prepared using procedures analogous to those described above for the synthesis of Compounds 4.001 and 4.002 using the appropriate starting materials which are available commercially or prepared using preparations well-known to those skilled in the art.

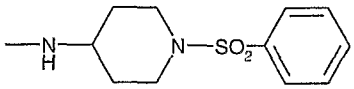
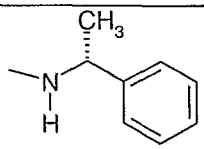
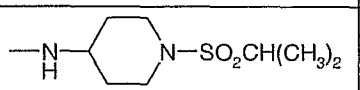
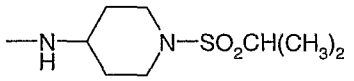
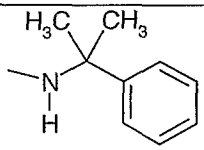
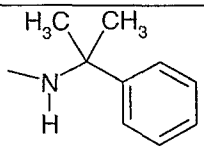
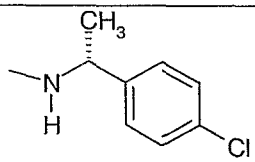
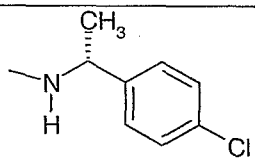
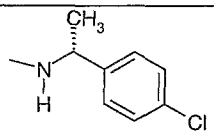
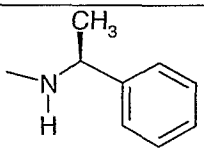
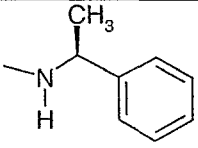
Table 4

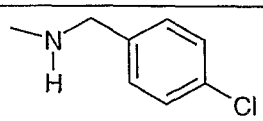
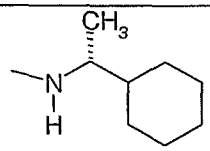
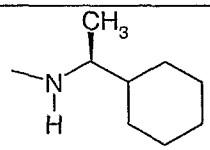
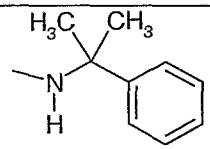
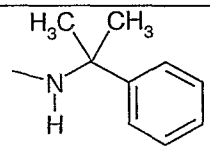
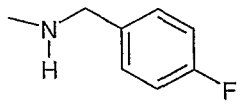
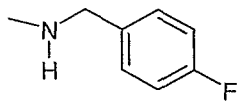
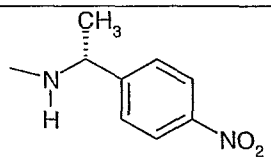
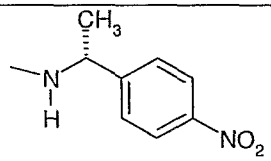
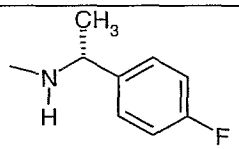
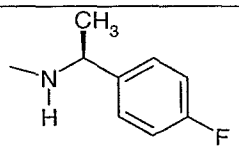


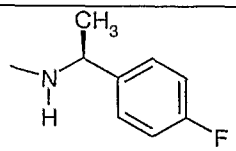
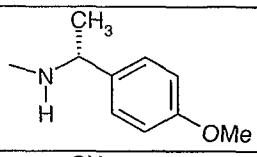
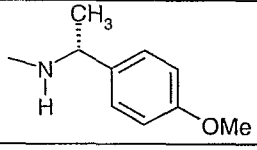
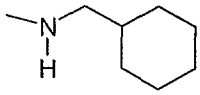
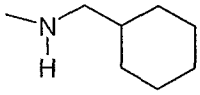
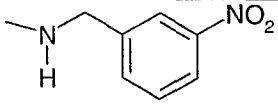
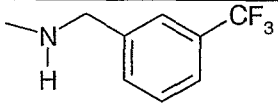
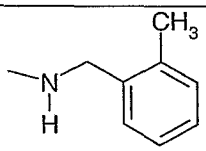
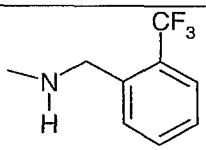
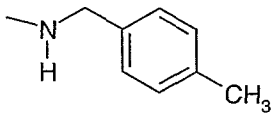
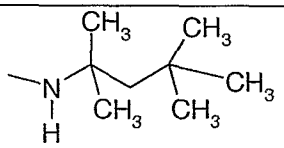
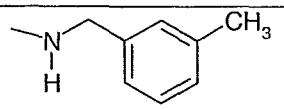
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)

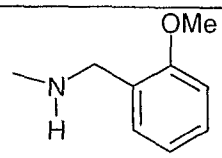
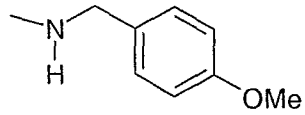
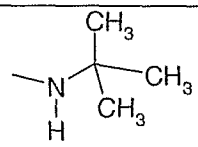
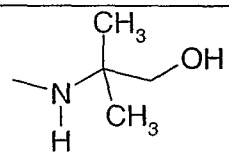
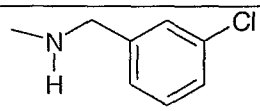
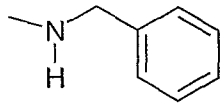
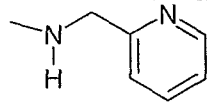
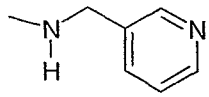
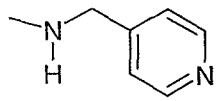
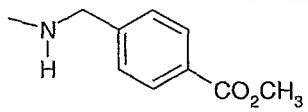
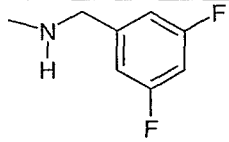
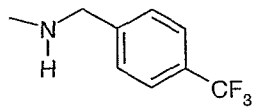
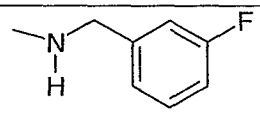
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.001[3h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		425
4.002[3h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		425
4.003[2h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		422
4.004[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		422
4.005[3h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		411
4.006[2h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		445
4.007[2h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		403
4.008[3h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		429
4.009[2h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		439
4.010[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		439
4.011[3h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		479
4.012[5h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		434
4.013[3h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		434
4.014[3h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		403
4.015[5h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		432

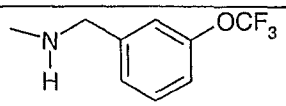
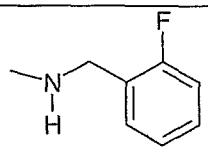
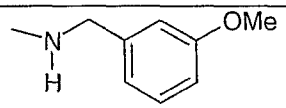
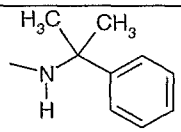
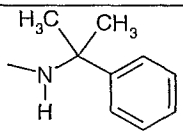
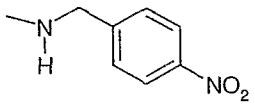
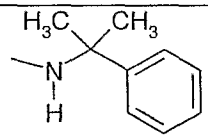
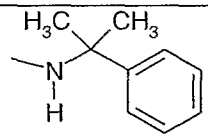
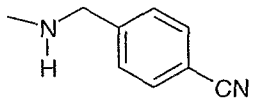
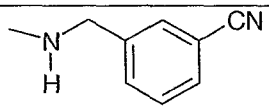
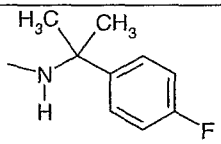
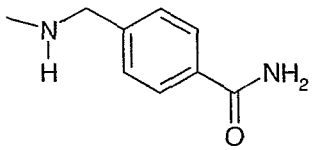
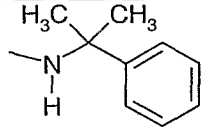
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.016[4h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		467
4.017[3h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		441
4.018[4h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		399
4.019[3h]	3R, 5S, 1'R	4-chloro-phenyl	2-chloro-phenyl		425
4.020[2h]	3S, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		425
4.021[3h]	MIX	4-chloro-phenyl	2-chloro-phenyl		494
4.022[4h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl	-NH-CH(CH_2CH_3)$_2$	391
4.023[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl	-NH-CH(CH_2CH_3)$_2$	391
4.024[3h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		480
4.025[5h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		480
4.026[4h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		391
4.027[4h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		448
4.028[3h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		544

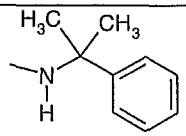
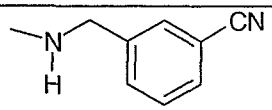
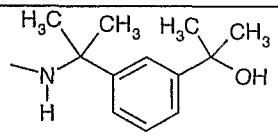
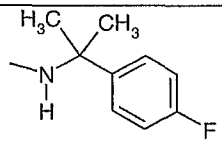
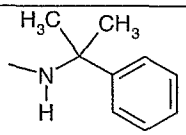
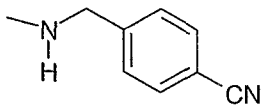
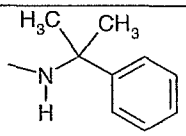
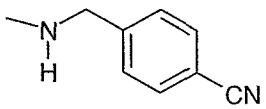
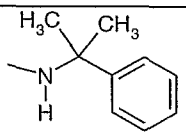
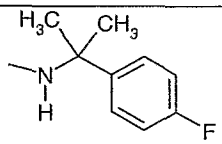
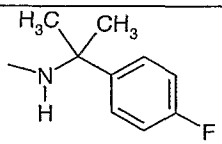
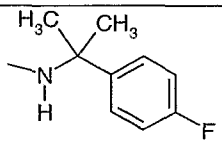
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.029[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		544
4.030[2h]	3R, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		425
4.031[2h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		510
4.032[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		510
4.033[3h]	3RS, 5SR	4-chloro-phenyl	2,4-dichloro-phenyl		473
4.034[2h]	3RS, 5RS	4-chloro-phenyl	2,4-dichloro-phenyl		473
4.035[2h]	3R, 5R, 1'S	4-chloro-phenyl	2-chloro-phenyl		459
4.036[3h]	3S, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		459
4.037[2h]	3R, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		459
4.038[2h]	3R, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		425
4.039[5h]	3S, 5S, 1'S	4-chloro-phenyl	2-chloro-phenyl		425

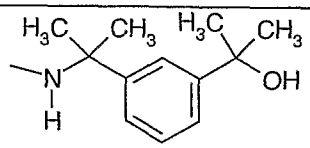
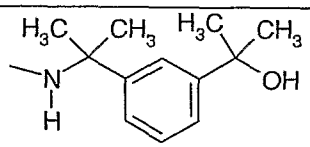
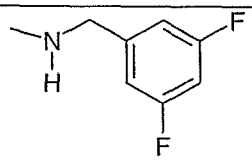
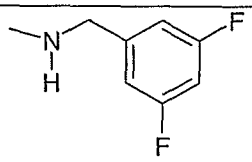
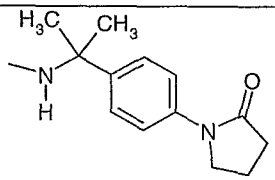
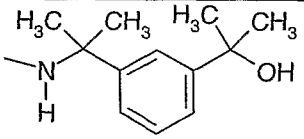
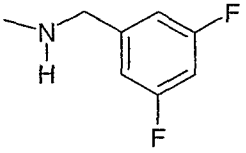
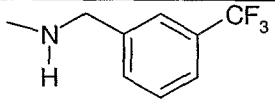
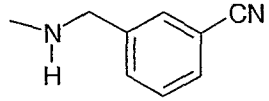
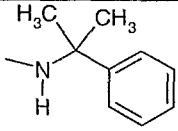
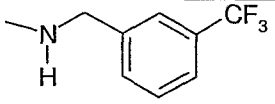
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.040[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		445
4.041[2h]	3R, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		431
4.042[2h]	3R, 5R, 1'S	4-chloro-phenyl	2-chloro-phenyl		431
4.043[1h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		439
4.044[2h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		439
4.045[3h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		429
4.046[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		429
4.047[2h]	3S, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		470
4.048[1h]	3R, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		470
4.049[2h]	3R, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		443
4.050[3h]	3S, 5R, 1'S	4-chloro-phenyl	2-chloro-phenyl		443

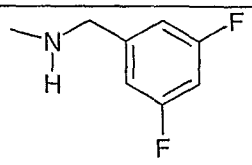
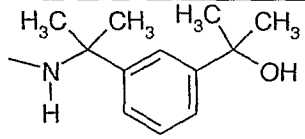
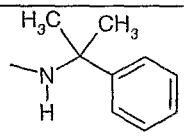
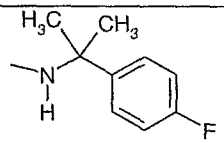
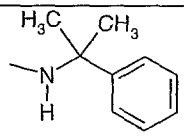
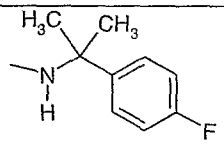
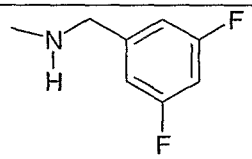
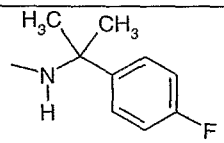
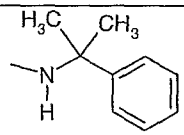
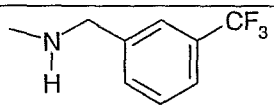
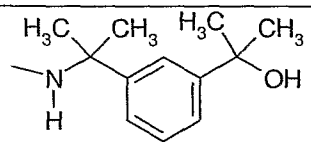
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.051[2h]	3R, 5R, 1'S	4-chloro-phenyl	2-chloro-phenyl		443
4.052[3h]	3S, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		455
4.053[2h]	3R, 5R, 1'R	4-chloro-phenyl	2-chloro-phenyl		455
4.054[3h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		417
4.055[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		417
4.056[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		456
4.057[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		479
4.058[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		425
4.059[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		479
4.060[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		425
4.061[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		433
4.062[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		425

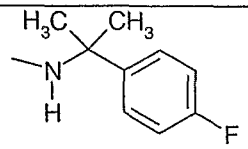
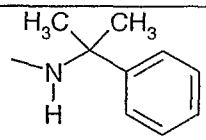
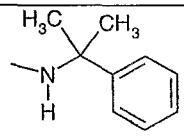
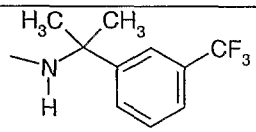
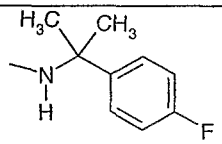
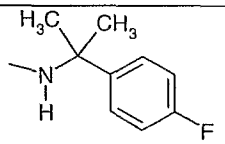
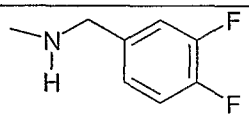
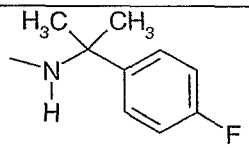
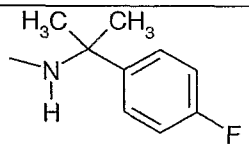
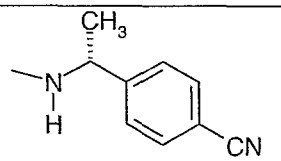
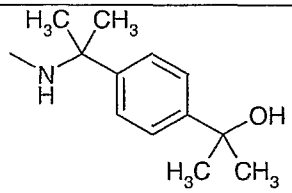
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.063[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		441
4.064[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		441
4.065[4h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		377
4.066[4h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		393
4.067[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		445
4.068[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		411
4.069[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		412
4.070[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		412
4.071[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		412
4.072[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		469
4.073[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		447
4.074[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		479
4.075[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		429

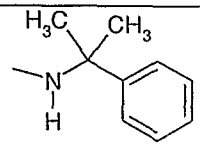
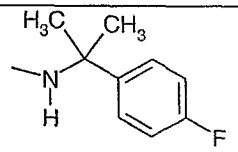
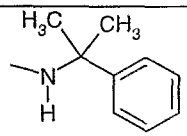
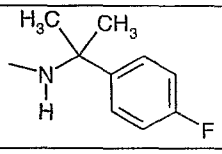
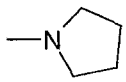
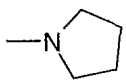
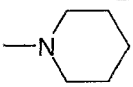
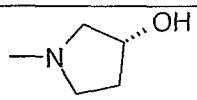
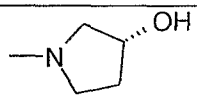
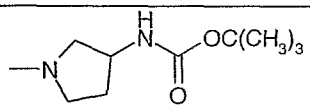
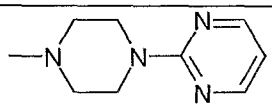
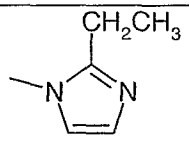
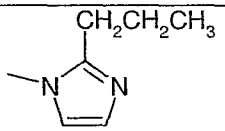
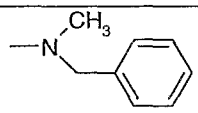
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.076[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		495
4.077[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		429
4.078[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		441
4.079[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-4-fluoro-phenyl		457
4.080[1h]	3RS, 5RS	4-chloro-phenyl	2,3-dichloro-phenyl		473
4.081[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		456
4.082[1h]	3RS, 5RS	4-chloro-phenyl	3-chloro-phenyl		439
4.083[2h]	3RS, 5SR	4-chloro-phenyl	3-chloro-phenyl		439
4.084[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		436
4.085[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		436
4.086[1h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		457
4.087[3h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		454
4.088[2h]	3RS, 5RS	4-chloro-phenyl	4-chloro-phenyl		439

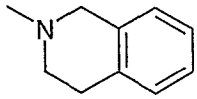
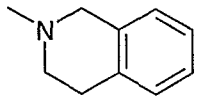
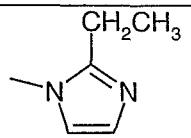
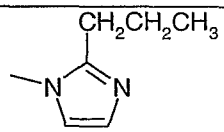
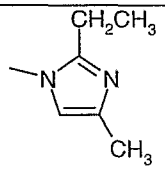
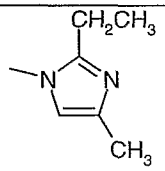
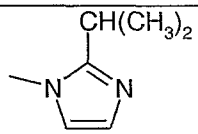
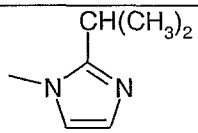
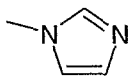
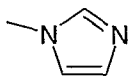
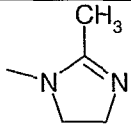
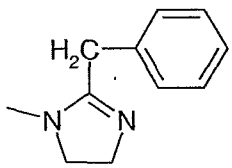
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.089[1h]	3R, 5R	4-cyano-phenyl	2-chloro-phenyl		430
4.090[2h]	3R, 5R	4-cyano-phenyl	2-chloro-phenyl		427
4.091[2h]	3R, 5R	4-cyano-phenyl	2-chloro-phenyl		488
4.092[1h]	3R, 5R	4-cyano-phenyl	2-chloro-phenyl		448
4.093[1h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		414
4.094[3h]	3RS, 5RS	4-cyano-phenyl	3-fluoro-phenyl		411
4.095[1h]	3RS, 5RS	4-cyano-phenyl	3-cyano-phenyl		421
4.096[3h]	3RS, 5RS	4-cyano-phenyl	3-cyano-phenyl		418
4.097[1h]	3R, 5R	4-cyano-phenyl	2-chloro-phenyl		430
4.098[1h]	3R, 5R	4-cyano-phenyl	2-chloro-phenyl		448
4.099[1h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		432
4.100[1h]	3RS, 5RS	4-cyano-phenyl	3-cyano-phenyl		439

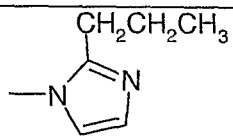
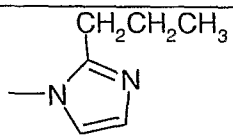
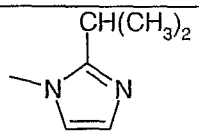
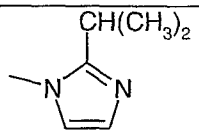
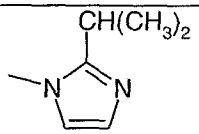
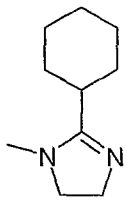
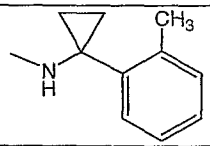
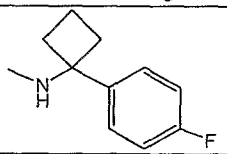
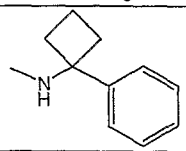
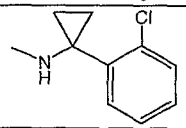
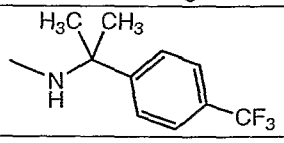
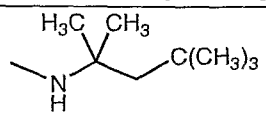
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.101[2h]	3RS, 5RS	4-cyano-phenyl	3-fluoro-phenyl		472
4.102[2h]	3RS, 5RS	4-cyano-phenyl	3-cyano-phenyl		479
4.103[2h]	3RS, 5RS	4-cyano-phenyl	3-fluoro-phenyl		422
4.104[2h]	3RS, 5RS	4-cyano-phenyl	3-cyano-phenyl		429
4.105[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		522
4.106[2h]	3RS, 5RS	4-chloro-phenyl	3-cyano-phenyl		488
4.107[2h]	3RS, 5RS	4-chloro-phenyl	3-cyano-phenyl		438
4.108[2h]	3RS, 5RS	4-cyano-phenyl	3-cyano-phenyl		461
4.109[2h]	3RS, 5RS	4-cyano-phenyl	3-chloro-phenyl		427
4.110[1h]	3RS, 5RS	4-cyano-phenyl	3-chloro-phenyl		430
4.111[2h]	3RS, 5RS	4-cyano-phenyl	3-chloro-phenyl		470

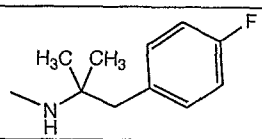
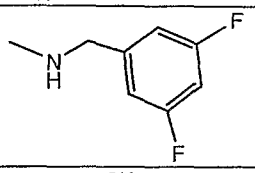
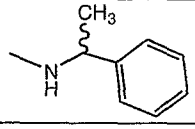
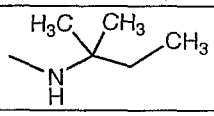
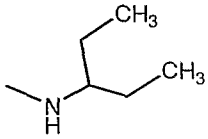
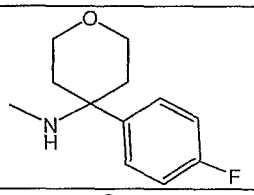
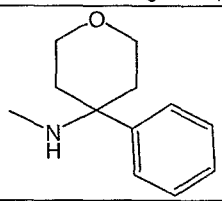
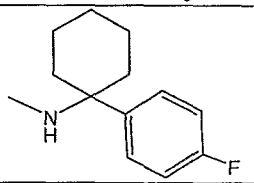
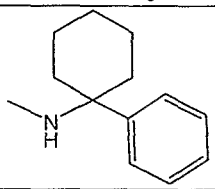
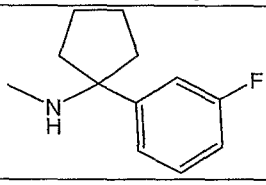
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.112[1h]	3RS, 5RS	4-cyano-phenyl	3-chloro-phenyl		438
4.113[1h]	3RS, 5RS	4-cyano-phenyl	3-chloro-phenyl		488
4.114[1h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		414
4.115[1h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		432
4.116[1h]	3R, 5R	4-cyano-phenyl	3-cyano-phenyl		421
4.117[1h]	3R, 5R	4-cyano-phenyl	3-cyano-phenyl		439
4.118[2h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		422
4.119[1h]	3RS, 5RS	4-chloro-phenyl	3-cyano-phenyl		448
4.120[1h]	3RS, 5RS	4-chloro-phenyl	3-cyano-phenyl		430
4.121[2h]	3RS, 5RS	4-chloro-phenyl	3-cyano-phenyl		470
4.122[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		497

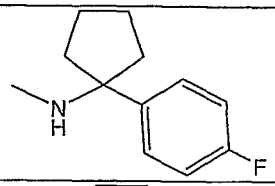
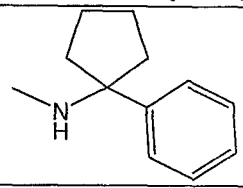
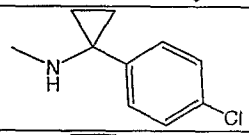
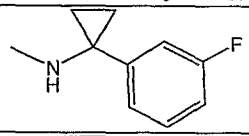
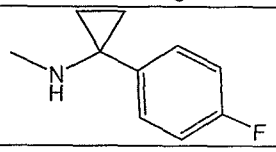
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.123[3h]	3S, 5S	4-fluoro-phenyl	3-cyano-phenyl		432
4.124[2h]	3S, 5S	4-fluoro-phenyl	3-cyano-phenyl		414
4.125[1h]	3RS, 5RS	5-chloro-2-pyridyl	3-chloro-phenyl		440
4.126[1h]	3R, 5R	4-chloro-phenyl	3-cyano-phenyl		498
4.127[3h]	3S, 5S	4-chloro-phenyl	3-cyano-phenyl		448
4.128[2h]	3R, 5R	4-chloro-phenyl	3-cyano-phenyl		448
4.129[3h]	3S, 5S	4-chloro-phenyl	3-cyano-phenyl		438
4.130[2h]	3R, 5R	4-fluoro-phenyl	3-cyano-phenyl		432
4.131[2h]	3R, 5R	4-chloro-phenyl	3-cyano-phenyl		448
4.132[5h]	3S, 5S, 1'R	4-cyano-phenyl	3-fluoro-phenyl		425
4.133[2h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		472

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.134[3h]	3RS, 5RS	3-cyano-phenyl	3-chloro-phenyl		430
4.135[1h]	3R, 5R	5-chloro-2-pyridyl	3-chloro-phenyl		458
4.136[9]	3R, 5R	5-chloro-2-pyridyl	3-bromo-phenyl		484
4.137[9]	3RS, 5RS	5-chloro-2-pyridyl	3-bromo-phenyl		502
4.138[4h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		389
4.139[5h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		391
4.140[5h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		391
4.141[6h]	3RS, 5SR, 3'R	4-chloro-phenyl	2-chloro-phenyl		490
4.142[5h]	3RS, 5RS, 3'R	4-chloro-phenyl	2-chloro-phenyl		468
4.143[5h]	3RS, 5SR, 3'R	4-chloro-phenyl	2-chloro-phenyl		400
4.144[5h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		414
4.145[2h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		425
4.146[2h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		437
4.147[3h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		437

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.148[4h]	3RS, 5SS	4-chloro-phenyl	2-chloro-phenyl		400
4.149[6h]	3RS, 5RR	4-chloro-phenyl	2-chloro-phenyl		414
4.150[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		414
4.151[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		414
4.152[3h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		414
4.153[2h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		414
4.154[4h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		372
4.155[2h]	3RS, 5RR	4-chloro-phenyl	2-chloro-phenyl		372
4.156[7h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		388
4.157[5h]	3RS, 5RS	4-chloro-phenyl	2-chloro-phenyl		464
4.158[8h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		448
4.159[3h]	3RS, 5SR	4-chloro-phenyl	2-chloro-phenyl		448

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.160[5h]	3RS, 5SR	4-chloro-phenyl	2,4-dichloro-phenyl		414
4.161[3h]	3RS, 5RS	4-chloro-phenyl	2,4-dichloro-phenyl		414
4.162[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		414
4.163[3h]	3S, 5S	4-chloro-phenyl	2-chloro-phenyl		456
4.164[5h]	3S, 5R	4-chloro-phenyl	2-chloro-phenyl		389
4.165[3h]	MIX	4-chloro-phenyl	2-chloro-phenyl		391
4.166[2h]		4-chloro-phenyl	2-chloro-phenyl		451
4.167[2h]		4-chloro-phenyl	2-chloro-phenyl		469
4.168[1h]		4-chloro-phenyl	2-chloro-phenyl		451
4.169[10h]		4-chloro-phenyl	2-chloro-phenyl		472
4.170[10h]		4-chloro-phenyl	2-chloro-phenyl		507
4.171[1h]		4-chloro-phenyl	2-chloro-phenyl		433

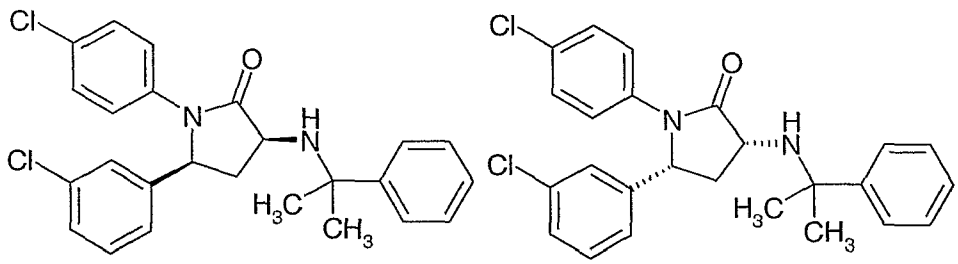
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.172[1h]		4-chloro-phenyl	2-chloro-phenyl		471
4.173[2h]		4-chloro-phenyl	2-chloro-phenyl		447
4.174[3h]		4-chloro-phenyl	2-chloro-phenyl		425
4.175[3h]		4-chloro-phenyl	2-chloro-phenyl		391
4.176[10h]		4-chloro-phenyl	2-chloro-phenyl		391
4.177[2h]		4-chloro-phenyl	2-chloro-phenyl		499
4.178[10h]		4-chloro-phenyl	2-chloro-phenyl		481
4.179[2h]		4-chloro-phenyl	2-chloro-phenyl		497
4.180[2h]		4-chloro-phenyl	2-chloro-phenyl		479
4.181[2h]		4-chloro-phenyl	2-chloro-phenyl		483

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
4.182[10h]		4-chloro-phenyl	2-chloro-phenyl		483
4.183[2h]		4-chloro-phenyl	2-chloro-phenyl		465
4.184[10h]		4-chloro-phenyl	2-chloro-phenyl		472
4.185[10h]		4-chloro-phenyl	2-chloro-phenyl		455
4.186[2h]		4-chloro-phenyl	2-chloro-phenyl		455

[1h]human.[1r]rat CB-1 binding Ki is < 1 nM
[2h]human, [2r]rat CB-1 binding Ki is < 10 nM
[3h]human, [3r]rat CB-1 binding Ki is < 50 nM
[4h]human, [4r]rat CB-1 binding Ki is <100 nM
[5h]human, [5r]rat CB-1 binding Ki is < 250 nM
[6h]human, [6r]rat CB-1 binding Ki is < 500 nM
[7h]human, [7r]rat CB-1 binding Ki is <1000 nM
[8h]human, [8r]rat CB-1 binding Ki is ≤ 4000 nM
[9]Data not available
[10h]human, no measurable binding

Example 5

(3S,5S)- and (3R,5R)-5-(3-chloro-phenyl)-1-(4-chloro-phenyl)-3-(1-methyl-1-phenyl-ethylamino)-pyrrolidin-2-one (5.01 and 5.02):



5.01 **5.02**

The racemic mixture from Example 4.082 was separated into the two enantiomers 5.01 and 5.02 by HPLC using the following conditions.

Column: Chiralcel OD, 10 cm x 25 cm

Racemic sample size: 340 mg

Loading solvent: 5 mL, 3:2 methanol:methylene chloride

Mobile phase: 95 heptane : 5 ethanol

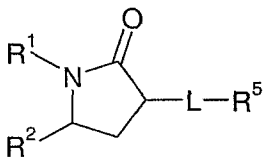
Flow rate: 250 mL/min

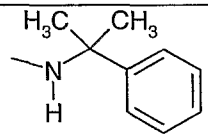
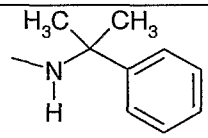
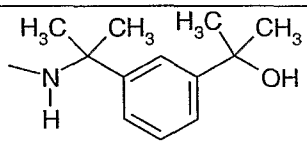
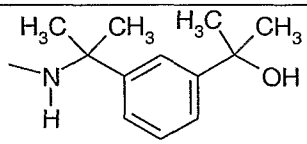
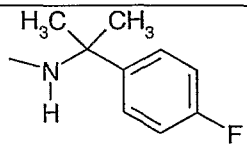
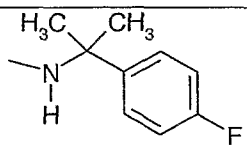
The retention times of the two enantiomers were 12 minutes (100% ee) for Example 5.01 (3S,5S enantiomer) and 22 minutes (100% ee) for Example 5.02 (3R,5R enantiomer). The yields were 156 mg for Example 5.01 and 157 mg for Example 5.02.

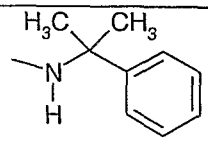
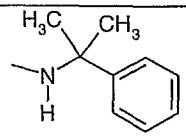
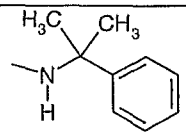
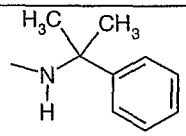
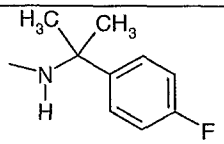
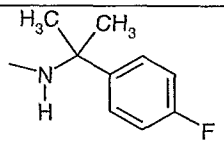
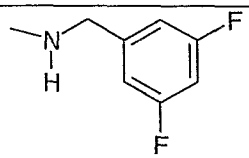
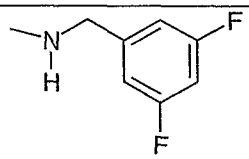
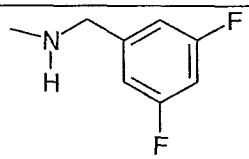
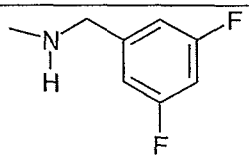
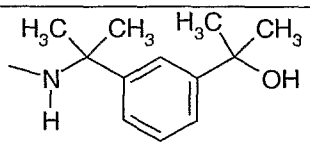
(3S,5S)-5-(3-chloro-phenyl)-1-(4-chloro-phenyl)-3-(1-methyl-1-phenyl-ethylamino)-pyrrolidin-2-one (Example 5.01): ^{1}H NMR ($CDCl_3$): 1.51 (s, 3H), 1.53 (s, 3H), 1.80 (dt, J = 12.5, 10.8 Hz, 1H), 2.62 (ddd, J = 12.5, 7.9, 6.0, 1H), 2.83 (bs, 1H), 3.38 (dd, J = 10.8, 7.9 Hz, 1H), 4.84 (dd, J = 10.0, 6.2 Hz, 1H), 7.00 (m, 1H), 7.12-7.25 (m, 8H), 7.33 (m, 2H), 7.50 (m, 2H). HRMS calcd for $C_{25}H_{25}Cl_2N_2O$ (MH+): 439.1338, found: 439.1345.

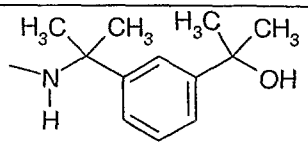
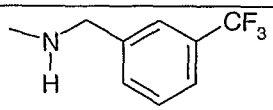
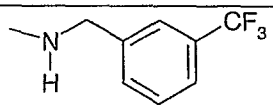
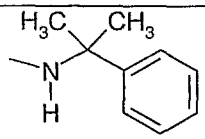
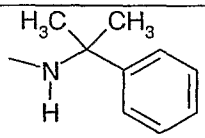
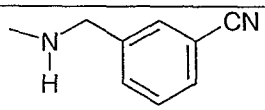
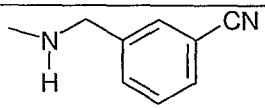
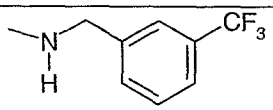
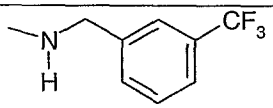
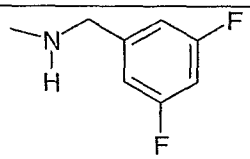
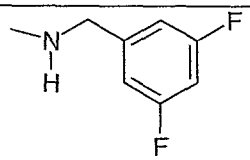
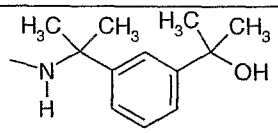
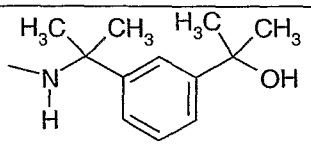
The following compounds listed in Table 5 were prepared from their cooresponding racemates in Example 4 or 1 using procedures analogous to those described above for the resolution of the racemate Example 4.082 into Compounds 5.01 and 5.02.

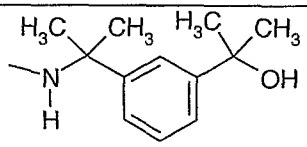
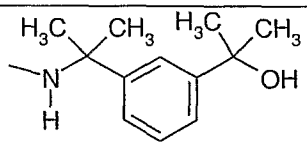
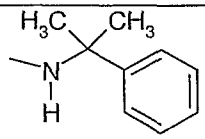
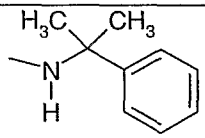
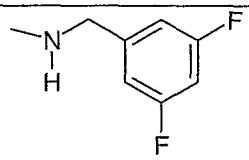
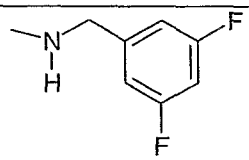
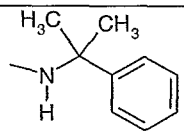
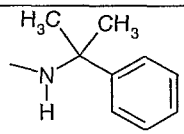
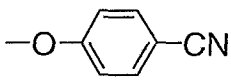
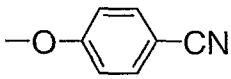
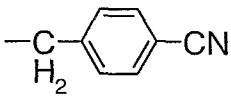
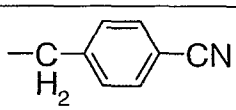
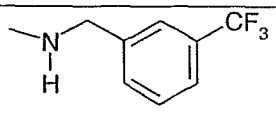
Table 5

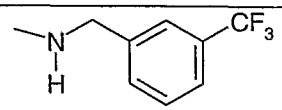


Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
5.01[3h]	3S, 5S	4-chloro-phenyl	3-chloro-phenyl		439
5.02[1h]	3R, 5R	4-chloro-phenyl	3-chloro-phenyl		439
5.03[3h]	3S, 5S	4-cyano-phenyl	3-fluoro-phenyl		472
5.04[1h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		472
5.05[2h]	3S, 5S	4-cyano-phenyl	3-cyano-phenyl		439
5.06[1h]	3R, 5R	4-cyano-phenyl	3-cyano-phenyl		439

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
5.07[2h]	3S, 5S	4-cyano-phenyl	3-fluoro-phenyl		414
5.08[1h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		414
5.09[2h]	3S, 5S	4-cyano-phenyl	3-cyano-phenyl		421
5.10[1h]	3R, 5R	4-cyano-phenyl	3-cyano-phenyl		421
5.11[2h]	3S, 5S	4-cyano-phenyl	3-fluoro-phenyl		432
5.12[1h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		432
5.13[5h]	3S, 5S	4-cyano-phenyl	3-fluoro-phenyl		422
5.14[2h]	3R, 5R	4-cyano-phenyl	3-fluoro-phenyl		422
5.15[5h]	3S, 5S	4-cyano-phenyl	3-cyano-phenyl		429
5.16[2h]	3R, 5R	4-cyano-phenyl	3-cyano-phenyl		429
5.17[3h]	3S, 5S	4-cyano-phenyl	3-cyano-phenyl		479

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
5.18[1h]	3R, 5R	4-cyano-phenyl	3-cyano-phenyl		479
5.19[3h]	3S, 5S	4-cyano-phenyl	3-cyano-phenyl		461
5.20[2h]	3R, 5R	4-cyano-phenyl	3-cyano-phenyl		461
5.21[3h]	3S, 5S	4-cyano-phenyl	3-chloro-phenyl		430
5.22[1h]	3R, 5R	4-cyano-phenyl	3-chloro-phenyl		430
5.23[3h]	3S, 5S	4-cyano-phenyl	3-chloro-phenyl		427
5.24[2h]	3R, 5R	4-cyano-phenyl	3-chloro-phenyl		427
5.25[3h]	3S, 5S	4-cyano-phenyl	3-chloro-phenyl		470
5.26[2h]	3R, 5R	4-cyano-phenyl	3-chloro-phenyl		470
5.27[4h]	3S, 5S	4-cyano-phenyl	3-chloro-phenyl		438
5.28[1h]	3R, 5R	4-cyano-phenyl	3-chloro-phenyl		438
5.29[2h]	3S, 5S	4-cyano-phenyl	3-chloro-phenyl		488
5.30[1h]	3R, 5R	4-cyano-phenyl	3-chloro-phenyl		488

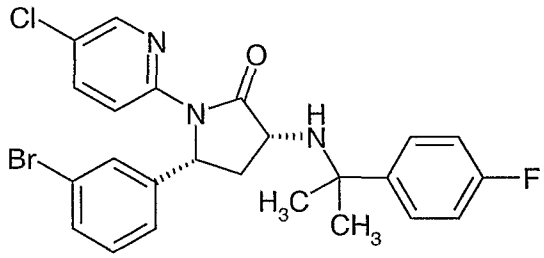
Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
5.31[3h]	3S, 5S	4-chloro-phenyl	3-cyano-phenyl		488
5.32[2h]	3R, 5R	4-chloro-phenyl	3-cyano-phenyl		488
5.33[3h]	3S, 5S	4-chloro-phenyl	3-cyano-phenyl		430
5.34[1h]	3R, 5R	4-chloro-phenyl	3-cyano-phenyl		430
5.35[4h]	3S, 5S	4-chloro-phenyl	3-cyano-phenyl		<u>438</u>
5.36[2h]	3R, 5R	4-chloro-phenyl	3-cyano-phenyl		<u>438</u>
5.37[3h]	3S, 5S	5-chloro-2-pyridyl	3-chloro-phenyl		440
5.38[1h]	3R, 5R	5-chloro-2-pyridyl	3-chloro-phenyl		440
5.39[3h]	3S,5S	4-chloro-phenyl	2-chloro-phenyl		423
5.40[2h]	3R, 5R	4-chloro-phenyl	2-chloro-phenyl		423
5.41[3h]	3R,5S	4-chloro-phenyl	4-chloro-phenyl		421
5.42[2h]	3S,5R	4-chloro-phenyl	4-chloro-phenyl		421
5.43[3h]	3S, 5S	3-chloro-phenyl	4-cyano-phenyl		470

Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
5.44[2h]	3R, 5R	3-chloro-phenyl	4-cyano-phenyl		470

[1h]human CB-1 binding Ki is < 1 nM
[2h]human CB-1 binding Ki is < 10 nM
[3h]human CB-1 binding Ki is < 50 nM
[4h]human CB-1 binding Ki is <100 nM
[5h]human CB-1 binding Ki is < 250 nM
[6h]human CB-1 binding Ki is < 500 nM
[7h]human CB-1 binding Ki is <1000 nM
[8h]human CB-1 binding Ki is ≤ 4000 nM

Example 6

Preparation of (3RS,5RS)-3-(2-(4-fluorophenyl)propan-2-ylamino)-5-(3-bromophenyl)-1-(5-chloropyridin-2-yl)pyrrolidin-2-one (6.01):



6.01

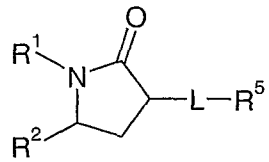
Step A. A solution of 1.37 g (3.7 mmol) of (5RS)-5-(3-bromophenyl)-1-(5-chloropyridin-2-yl)-1H-pyrrolidin-2,3-dione (Step A in the preparation of I-10a), 575 mg (3.7 mmol) 2-(4-fluorophenyl)propan-2-amine and 125 mL of benzene was refluxed under a Dean-Stark trap for 16 hours. The solution was cooled to room temperature and concentrated to give 1.87 g of the enamine which was used without further purification in the next step.

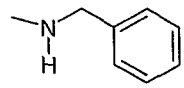
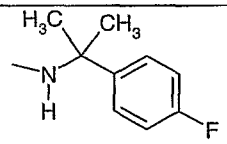
Step B. A solution of 1.87 g (6.37 mmol) of the enamine from Step A, 0.43 mL (7.46 mmol) of acetic acid and 469 mg (7.46 mol) of sodium cyanoborohydride in 37 mL was prepared at 0°C and allowed to return to ambient temperature. An additional 0.43 mL (7.46 mmol) of acetic acid and 469 mg (7.46 mol) of sodium cyanoborohydride were added and the reaction was allowed to stir for 16 hours. The reaction mixture was concentrated *in vacuo*, the residue dissolved in water and chloroform. Sodium bicarbonate solution was added to basify and the mixture was extracted with chloroform (2x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated to give 1.78 g of crude product. Purification by MPLC with 5% EtOAc : 95% hexane over 15 min, then 5% EtOAc : 95% hexane to 25% EtOAc : 75% hexane over 30 min gave 806 mg (54%) of the title compound (6.01). ^{1}H NMR ($CDCl_3$): 1.50 (s, 6H), 1.75 (dt, J = 12.9, 8.3, 6.6 Hz, 1H), 2.63 (bs, 1H), 3.40 (dd, J = 10.8, 8.3 Hz,1H), 5.18 (dd, J = 10.2, 6.4 Hz, 1H), 7.00 (m, 2H), 7.09 (m, 2H), 7.3-7.5 (m, 4H), (7.61 (dd, J = 8.6, 2.5 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H).

The following compounds listed in Table 6 were prepared using procedures analogous to those described above for the synthesis of Compound 6.01 using the appropriate starting

materials which are available commercially or prepared using preparations well-known to those skilled in the art.

Table 6

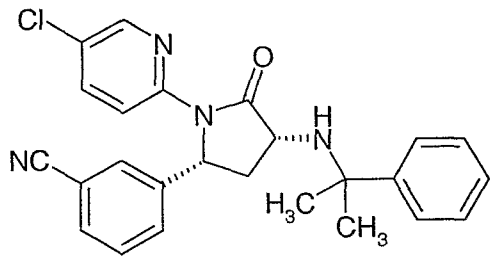


Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
6.01[2h]	3RS,5RS	5-chloro-2-pyridyl	3-bromo-phenyl		484
6.02[1h]	3RS,5RS	5-chloro-2-pyridyl	3-bromo-phenyl		502

[1h]human CB-1 binding Ki is < 1 nM [2h]human CB-1 binding Ki is < 10 nM

Example 7

Preparation of (3R,5R)-1-(5-chloropyridin-2-yl)-5-(3-cyanophenyl)-3-(1-methyl-1-phenyl-ethylamino)-pyrrolidin-2-one (7.01):



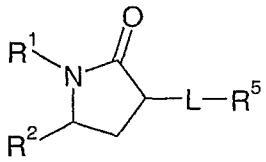
7.01

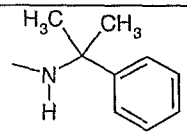
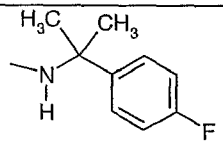
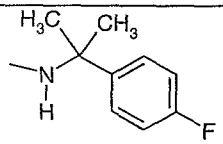
A mixture of 0.051 g (0.105 mmol) of (3R,5R)-1-(5-chloropyridin-2-yl)-5-(3-bromophenyl)-3-(1-methyl-1-phenyl-ethylamino)-pyrrolidin-2-one (Example 4.136), 0.025 g (0.21 mmol) of zinc cyanide and 0.121 g (0.105 mmol) of $Pd(PPh_3)_4$ in 2 mL of dry THF in a dry, degreased round-bottom flask and heated at 55°C for 3 hours. The mixture was cooled to room temperature, diluted with water, extracted with EtOAc (3x), the combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by MPLC with 25% EtOAc : 75% hexane at 20 mL/minute, 10 mL/tube for 25 min gave 29 mg (64%) of the title compound (7.01). ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 3H), 1.53 (s, 1H), 1.75 (dt, J = 12.9, 10.4 Hz, 1H), 2.61 (ddd, J = 14.9, 8.3, 6.6 Hz, 1H), 3.44 (dd, J = 10.4, 8.3 Hz, 1H), 5.52 (dd, J = 10.0, 6.6 Hz, 1H), 7.22 (m, 1H), 7.3-7.5 (m, 7H), 7.62 (dd, J = 8.7, 2.5 Hz, 1H), 7.97 (d, J = 2.1 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H).

The following compounds listed in Table 7 were prepared using procedures analogous to those described above for the synthesis of Compound 7.01 using the appropriate starting

materials which are available commercially or prepared using preparations well-known to those skilled in the art.

Table 7

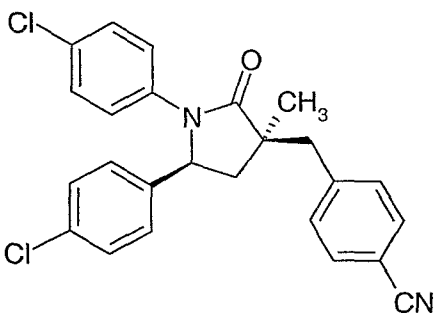


Ex. No.	Stereo-chem	R^1	R^2	L-R^5	MS (M+H)
7.01[1h]	3R, 5R	5-chloro-2-pyridyl	3-cyano-phenyl		431
7.02[9]	3RS, 5RS	5-chloro-2-pyridyl	3-cyano-phenyl		449
7.03[1h]	3R, 5R	5-chloro-2-pyridyl	3-cyano-phenyl		449

[1h]human CB-1 binding Ki is < 1 nM [9]Data not available

Example 8

Preparation of (3RS,5RS)-1-(4-chlorophenyl)-5-(4-chlorophenyl)-3-((4-cyano-phenyl)methyl)-3-methyl-pyrrolidin-2-one (8.01):



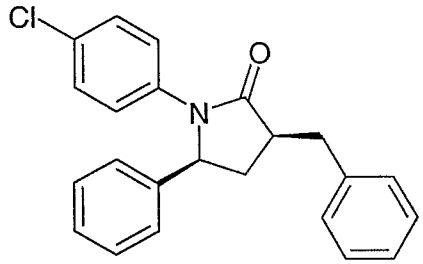
8.01

A solution of 0.231 g (0.548 mmol) of (3RS,5SR)-1-(4-chlorophenyl)-5-(4-chlorophenyl)-3-((4-cyano-phenyl)methyl)-pyrrolidin-2-one (Example 3.18) in 6 mL THF was chilled to -78°C, treated with 0.41 mL of LDA (2.0 M in THF) and allowed to stir for 30 minutes. A solution of 86 mg (0.60 mmol) of methyl iodide in 4 mL THF was added dropwise. The mixture was kept at -78°C for an additional 1 hour, then allowed to warm to ambient temperature over 16 hours. The reaction was quenched with satd ammonium chloride, diluted with water and extracted with ethyl acetate (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purificaiton was accomplished by silica gel MPLC with a solvent gradient from 10% ethyl acetate : 90% hexane to 40% ethyl acetate : 60% hexane over 30 minutes gave 41 mg

(17%) of the title compound (8.01). ^{1}H NMR ($CDCl_3$): δ 1.35 (s, 3H), 1.85 (dd, J = 13.3, 8.7 Hz, 1H), 2.26 (dd, J = 13.3, 7.5 Hz, 1H), 2.80 (d, J = 13.3 Hz, 1H), 3.31 (d, J = 13.3, 1H), 5.06 (dd, J = 8.3, 7.5 Hz, 1H), 6.68 (m, 2H), 7.1-7.2 (m, 6H), 7.34 (bd, J = 8.3, 2H), 7.60 (bd, J = 8.3, 2H). MS 435 (M+H).

Example 9

Preparation of (3RS,5RS)-1-(4-chlorophenyl)-5-(phenyl)-3-phenylmethyl-pyrrolidin-2-one (9.01):

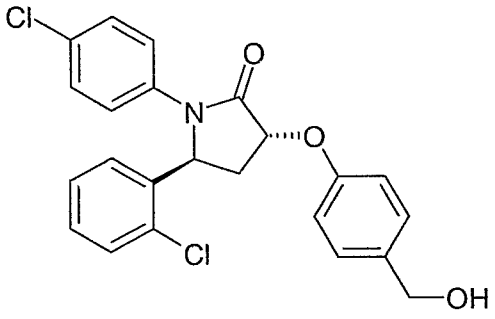


9.01

A solution of 100 mg (0.276 mmol) of (3SR,5RS)-1-(4-chlorophenyl)-5-(phenyl)-3-phenylmethyl-pyrrolidin-2-one (Example 3.02) in 1 mL THF was chilled to -78°C and treated with 0.28 mL (0.55 mmol) of LDA (2.0 M in THF). The mixture stirred for 1 hour at -78°C and was allowed to warm to ambient temperature over 16 hours. The reaction was quenched with satd ammonium chloride, diluted with water, extracted with ethyl acetate (3x), and washed with brine. The organic phase was dried (magnesium sulfate), filtered and evaporated. Purification by silica gel MPLC with a solvent gradient 5% ethyl acetate : 95% hexane to 30% ethyl acetate : 70% hexane over 30 minutes gave 26 mg (26%) of the title compound (9.01: 3RS,5RS; cis isomer). ^{1}H NMR ($CDCl_3$): δ 1.72 (ddd, J = 13.3, 10.5, 8.7 Hz, 1H), 2.59 (ddd, J = 13.3, 8.7, 7.1 Hz, 1H), 2.86 (dd, J = 13.5, 9.3 Hz, 1H), 2.98 (m, 1H), 3.36 (dd, J = 13.7, 3.7 Hz, 1H), 5.04 (dd, J = 8.7, 7.1 Hz, 1H), 6.98 (m, 2H), 7.15-7.30 (m, 12H). 3SR,5RRS; trans isomer recovered: ^{1}H NMR ($CDCl_3$): δ 2.03 (ddd, J = 12.6, 8.3, 2.7 Hz, 1H), 2.34 (ddd, J = 12.6, 9.6, 8.5 Hz, 1H), 2.82 (dd, J = 13.7, 8.7 Hz, 1H), 3.04 (m, 1H), 3.30 (dd, J = 13.7, 4.2 Hz, 1H), 4.93 (dd, J = 8.5, 2.7 Hz, 1H), 7.09 (m, 2H), 7.15-7.30 (m, 10H), 7.42 (m, 2H). MS 362 (M+H).

Example 10

Preparation of (3RS,5SR)-1-(4-chlorophenyl)-5-(2-chlorophenyl)-3-[4-(hydroxymethyl)phenoxy]pyrrolidin-2-one (10.01):



10.01

A solution of 100 mg (0.235 mmol) of 4-{[(3RS,5SR)-1-(4-chlorophenyl)-5-(2-chlorophenyl)-2-oxopyrrolidin-3-yl]oxy}benzaldehyde (Example 1.37) in 1 mL methanol was treated with 9 mg (0.23 mmol) of sodium borohydride. After 1 hour at ambient temperature, the mixture was diluted with water and extracted with ethyl acetate (3x). The combined organic layers were dried (magnesium sulfate), filtered and evaporated. Purification by silica gel MPLC with 30% ethyl acetate : 70% hexane gave 66 mg (66%) of the title compound (10.01). ^{1}H NMR ($CDCl_3$): 2.60 (ddd, J = 13.3, 7.7, 2.5 Hz, 1H), 2.76 (dt, J = 13.3, 8.3 Hz, 1H), 4.60 (s, 2H), 5.06 (t, J = 8.1, 1H), 5.69 (dd, J = 8.4, 2.3 Hz, 1H), 7.01 (m, 2H), 7.04 (dd, J = 7.9, 1.9 Hz, 1H), 7.2-7.3 (m, 6H), 7.45 (dd, J = 7.9, 1.3 Hz, 1H), 7.50 (m, 2H). HRMS calcd for $C_{23}H_{20}Cl_2NO_3$ (M+H): 428.0820, found: 428.0814.

PHARMACOLOGICAL TESTING

The utility of the compounds of the present invention in the practice of the instant invention can be evidenced by activity in at least one of the protocols described hereinbelow. The following acronyms are used in the protocols described below.

BSA - bovine serum albumin
DMSO - dimethylsulfoxide
EDTA - ethylenediamine tetracetic acid
PBS – phosphate-buffered saline
EGTA - ethylene glycol-*bis*(β-aminoethyl ether) N,N,N',N'-tetraacetic acid
GDP - guanosine diphosphate
sc - subcutaneous
po - orally
ip - intraperitoneal
icv - intra cerebro ventricular
iv - intravenous

[^{3}H]SR141716A - radiolabeled N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride available from Amersham Biosciences, Piscataway, NJ.

[^{3}H]CP-55940 - radiolabled 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol available from NEN Life Science Products, Boston, MA.

AM251 - *N* -(piperidin-1-yl)-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-1H-pyrazole-3-carboxamide available from Tocris™, Ellisville, MO.

All of the compounds listed in the Example section above were tested in the CB-1 receptor binding assay below (except Examples 4.136, 4.137 and 7.02). The compounds provided a range of human or rat binding activities from 0.08 nM to 4000 nM (See, Tables 1-7), with the exception of Examples 4.169, 4.170, 4.176, 4.178, 4.182, 4.184 and 4.185 which

showed no measurable human binding activity. No binding data is available for Examples 4.136, 4.137 and 7.02. Selected compounds having an activity <20 nM were then tested in the CB-1 GTPγ [^{35}S] Binding Assay and the CB-2 binding assay described below in the Biological Binding Assays section. Selected compounds were then tested *in vivo* using one or more of the functional assays described in the Biological Functional Assays section below.

In Vitro Biological Assays

Bioassay systems for determining the CB-1 and CB-2 binding properties and pharmacological activity of cannabinoid receptor ligands are described by Roger G. Pertwee in "Pharmacology of Cannabinoid Receptor Ligands" Current Medicinal Chemistry, **6**, 635-664 (1999) and in WO 92/02640 (U.S. Application No. 07/564,075 filed August 8, 1990, incorporated herein by reference).

The following assays were designed to detect compounds that inhibit the binding of [^{3}H] SR141716A (selective radiolabeled CB-1 ligand) and [^{3}H] 5-(1,1-dimethylheptyl)-2-[5-hydroxy-2-(3-hydroxypropyl)-cyclohexyl]-phenol; radiolabeled CB-1/CB-2 ligand) to their respective receptors.

Rat CB-1 Receptor Binding Protocol

PelFreeze brains (available from Pel Freeze Biologicals, Rogers, Arkansas) were cut up and placed in tissue preparation buffer (5 mM Tris HCl, pH = 7.4 and 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000 X g for 5 minutes at 4°C. The supernatant was recovered and centrifuged at 100,000 X G for 1 hour at 4°C. The pellet was then re-suspended in 25 ml of TME (25 nM Tris, pH = 7.4, 5 mM $MgCl_2$, and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [^{3}H] SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. A BCA protein assay was used to determine the appropriate tissue concentration and then 200 µl of rat brain tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 20°C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

Human CB-1 Receptor Binding Protocol

Human embryonic kidney 293 (HEK 293) cells transfected with the CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in homogenization buffer (10 mM EDTA, 10 mM EGTA, 10 mM Na Bicarbonate, protease inhibitors; pH = 7.4), and homogenized with a Dounce Homogenizer. The homogenate was then spun at 1,000X g for 5

minutes at 4°C. The supernatant was recovered and centrifuged at 25,000X G for 20 minutes at 4°C. The pellet was then re-suspended in 10 ml of homogenization buffer and re-spun at 25,000X G for 20 minutes at 4°C. The final pellet was re-suspended in 1 ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM $MgCl_2$ and 1 mM EDTA). A protein assay was performed and 200 µl of tissue totaling 20 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO and TME) and then 25 µl were added to a deep well polypropylene plate. [^{3}H] SR141716A was diluted in a ligand buffer (0.5% BSA plus TME) and 25 µl were added to the plate. The plates were covered and placed in an incubator at 30°C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. In the morning the filters were counted on a Wallac Betaplate™ counter (available from PerkinElmer Life Sciences™, Boston, MA).

CB-2 Receptor Binding Protocol

Chinese hamster ovary-K1 (CHO-K1) cells transfected with CB-2 cDNA (obtained from Dr. Debra Kendall, University of Connecticut) were harvested in tissue preparation buffer (5 mM Tris-HCl buffer (pH = 7.4) containing 2 mM EDTA), polytroned at high speed and kept on ice for 15 minutes. The homogenate was then spun at 1,000X g for 5 minutes at 4°C. The supernatant was recovered and centrifuged at 100,000X G for 1 hour at 4°C. The pellet was then re-suspended in 25 ml of TME (25 mM Tris buffer (pH = 7.4) containing 5 mM $MgCl_2$ and 1 mM EDTA) per brain used. A protein assay was performed and 200 µl of tissue totaling 10 µg was added to the assay.

The test compounds were diluted in drug buffer (0.5% BSA, 10% DMSO, and 80.5% TME) and then 25 µl were added to the deep well polypropylene plate. [^{3}H] 5-(1,1-Dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol was diluted a ligand buffer (0.5% BSA and 99.5% TME) and then 25 µl were added to each well at a concentration of 1 nM. A BCA protein assay was used to determine the appropriate tissue concentration and 200 µl of the tissue at the appropriate concentration was added to the plate. The plates were covered and placed in an incubator at 30°C for 60 minutes. At the end of the incubation period 250 µl of stop buffer (5% BSA plus TME) was added to the reaction plate. The plates were then harvested by Skatron format onto GF/B filtermats presoaked in BSA (5 mg/ml) plus TME. Each filter was washed twice. The filters were dried overnight. The filters were then counted on the Wallac Betaplate™ counter.

CB-1 GTPγ [^{35}S] Binding Assay

Membranes were prepared from CHO-K1 cells stably transfected with the human CB-1 receptor cDNA. Membranes were prepared from cells as described by Bass et al, in "Identification and characterization of novel somatostatin antagonists," Molecular Pharmacology, **50**, 709-715 (1996). GTPγ [^{35}S] binding assays were performed in a 96 well FlashPlate™ format

in duplicate using 100 pM GTPγ[^{35}S] and 10 μg membrane per well in assay buffer composed of 50 mM Tris HCl, pH 7.4, 3 mM $MgCl_2$, pH 7.4, 10 mM $MgCl_2$, 20 mM EGTA, 100 mM NaCl, 30 μM GDP, 0.1 % bovine serum albumin and the following protease inhibitors: 100 μg/ml bacitracin, 100 μg/ml benzamidine, 5 μg/ml aprotinin, 5 μg/ml leupeptin. The assay mix was then incubated with increasing concentrations of antagonist (10^{-10} M to 10^{-5} M) for 10 minutes and challenged with the cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (10 μM). Assays were performed at 30^0C for one hour. The FlashPlates™ were then centrifuged at 2000Xg for 10 minutes. Stimulation of GTPγ[^{35}S] binding was then quantified using a Wallac Microbeta.EC_{50} calculations done using Prism™ by Graphpad.

Inverse agonism was measured in the absense of agonist.

CB-1 FLIPR-based Functional Assay Protocol

CHO-K1 cells co-transfected with the human CB-1 receptor cDNA (obtained from Dr. Debra Kendall, University of Connecticut) and the promiscuous G-protein G16 were used for this assay. Cells were plated 48 hours in advance at 12500 cells per well on collagen coated 384 well black clear assay plates. Cells were incubated for one hour with 4μM Fluo-4 AM (Molecular Probes) in DMEM (Gibco) containing 2.5 mM probenicid and pluronic acid (.04%). The plates were then washed 3 times with HEPES-buffered saline (containing probenicid; 2.5 mM) to remove excess dye. After 20 min the plates were added to the FLIPR individually and fluorescence levels was continuously monitored over an 80 s period. Compound additions were made simultaneously to all 384 wells after 20 s of baseline. Assays were performed in triplicate and 6 point concentration-response curves generated. Antagonist compounds were subsequently challenged with 3μM WIN 55,212-2 (agonist). Data were analyzed using Graph Pad Prism.

Detection of Inverse Agonists

The following cyclic-AMP assay protocol using intact cells was used to determine inverse agonist activity.

Cells were plated into a 96-well plate at a plating density of 10,000-14,000 cells per well at a concentration of 100 μl per well. The plates were incubated for 24 hours in a 37°C incubator. The media was removed and media lacking serum (100 μl) was added. The plates were then incubated for 18 hours at 37°C.

Serum free medium containing 1 mM IBMX was added to each well followed by 10 μl of test compound (1:10 stock solution (25 mM compound in DMSO) into 50% DMSO/PBS) diluted 10X in PBS with 0.1% BSA. After incubating for 20 minutes at 37°C, 2 μM of Forskolin was added and then incubated for an additional 20 minutes at 37°C. The media was removed, 100 μl of 0.01N HCl was added and then incubated for 20 minutes at room temperature. Cell lysate (75 μl) along with 25 μl of assay buffer (supplied in FlashPlate™ cAMP assay kit available from NEN Life Science Products Boston, MA) into a Flashplate. cAMP standards and cAMP tracer were

added following the kit's protocol. The flashplate was then incubated for 18 hours at 4°C. The content of the wells were aspirated and counted in a Scintillation counter.

In Vivo Biological Assays

Cannabinoid agoinists such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenolhave been shown to affect four characteristic behaviors in mice, collectively known as the Tetrad. For a description of these behaviors see: Smith, P.B., et al. in "The pharmacological activity of anandamide, a putative endogenous cannabinoid, in mice." J. Pharmacol. Exp. Ther., **270**(1), 219-227 (1994) and Wiley, J., et al. in "Discriminative stimulus effects of anandamide in rats," Eur. J. Pharmacol., **276**(1-2), 49-54 (1995). Reversal of these activities in the Locomotor Activity, Catalepsy, Hypothermia, and Hot Plate assays described below provides a screen for *in vivo* activity of CB-1 antagonists.

All data is presented as % reversal from agonist alone using the following formula: (5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol/agonist - vehicle/agonist)/(vehicle/vehicle - vehicle/agonist). Negative numbers indicate a potentiation of the agonist activity or non-antagonist activity. Positive numbers indicate a reversal of activity for that particular test.

Locomotor Activity

Male ICR mice (n=6) (17-19 g, Charles River Laboratories, Inc., Wilmington, MA) were pre-treated with test compound (sc, po, ip, or icv). Fifteen minutes later, the mice were challenged with 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Twenty-five minutes after the agonist injection, the mice were placed in clear acrylic cages (431.8 cm x 20.9 cm x 20.3 cm) containing clean wood shavings. The subjects were allowed to explore surroundings for a total of about 5 minutes and the activity was recorded by infrared motion detectors (available from Coulbourn Instruments™, Allentown, PA) that were placed on top of the cages. The data was computer collected and expressed as "movement units."

Catalepsy

Male ICR mice (n=6)(17-19 g upon arrival) were pre-treated with test compound (sc, po, ip or icv). Fifteen minutes later, the mice were challenged with 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Ninety minutes post injection, the mice were placed on a 6.5 cm steel ring attached to a ring stand at a height of about 12 inches. The ring was mounted in a horizontal orientation and the mouse was suspended in the gap of the ring with fore- and hind-paws gripping the perimeter. The duration that the mouse remained completely motionless (except for respiratory movements) was recorded over a 3-minute period.

The data were presented as a percent immobility rating. The rating was calculated by dividing the number of seconds the mouse remains motionless by the total time of the observation period and multiplying the result by 100. A percent reversal from the agonist was then calculated.

Hypothermia

Male ICR mice (n=5) (17-19 g upon arrival) were pretreated with test compounds (sc, po, ip or icv). Fifteen minutes later, mice were challenged with the cannabinoid agonist 5-(1,1-

dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Sixty-five minutes post agonist injection, rectal body temperatures were taken. This was done by inserting a small thermostat probe approximately 2- 2.5 cm into the rectum. Temperatures were recorded to the nearest tenth of a degree

Hot Plate

Male ICR mice (n=7) (17-19 g upon arrival) are pre-treated with test compounds (sc, po, ip or iv). Fifteen minutes later, mice were challenged with a cannabinoid agonist 5-(1,1-dimethyl-heptyl)-2-[5-hydroxy-2-(3-hydroxy-propyl)-cyclohexyl]-phenol (sc). Forty-five minutes later, each mouse was tested for reversal of analgesia using a standard hot plate meter (Columbus Instruments). The hot plate was 10" x 10" x 0.75" with a surrounding clear acrylic wall. Latency to kick, lick or flick hindpaw or jump from the platform was recorded to the nearest tenth of a second. The timer was experimenter activated and each test had a 40 second cut off. Data were presented as a percent reversal of the agonist induced analgesia.

Food Intake

The following screen was used to evaluate the efficacy of test compounds for inhibiting food intake in Sprague-Dawley rats after an overnight fast.

Male Sprague-Dawley rats were obtained from Charles River Laboratories, Inc. (Wilmington, MA). The rats were individually housed and fed powdered chow. They were maintained on a 12 hour light/dark cycle and received food and water *ad libitum*. The animals were acclimated to the vivarium for a period of one week before testing was conducted. Testing was completed during the light portion of the cycle.

To conduct the food intake efficacy screen, rats were transferred to individual test cages without food the afternoon prior to testing, and the rats were fasted overnight. After the overnight fast, rats were dosed the following morning with vehicle or test compounds. A known antagonist was dosed (3 mg/kg) as a positive control, and a control group received vehicle alone (no compound). The test compounds were dosed at ranges between 0.1 and 100 mg/kg depending upon the compound. The standard vehicle was 0.5% (w/v) methylcellulose in water and the standard route of administration was oral. However, different vehicles and routes of administration were used to accommodate various compounds when required. Food was provided to the rats 30 minutes after dosing and the Oxymax automated food intake system (Columbus Instruments, Columbus, Ohio) was started. Individual rat food intake was recorded continuously at 10-minute intervals for a period of two hours. When required, food intake was recorded manually using an electronic scale; food was weighed every 30 minutes after food was provided up to four hours after food was provided. Compound efficacy was determined by comparing the food intake pattern of compound-treated rats to vehicle and the standard positive control.

Alcohol Intake

The following protocol evaluates the effects of alcohol intake in alcohol preferring (P) female rats (bred at Indiana University) with an extensive drinking history. The following

references provide detailed descriptions of P rats: Li ,T.-K., et al., "Indiana selection studies on alcohol related behaviors" in Development of Animal Models as Pharmacogenetic Tools (eds McClearn C. E., Deitrich R. A. and Erwin V. G.), Research Monograph 6, 171-192 (1981) NIAAA, ADAMHA, Rockville, MD; Lumeng, L, et al., "New strains of rats with alcohol preference and nonpreference" Alcohol And Aldehyde Metabolizing Systems, **3**, Academic Press, New York, 537-544 (1977); and Lumeng, L, et al., "Different sensitivities to ethanol in alcohol-preferring and -nonpreferring rats," Pharmacol, Biochem Behav., **16**, 125-130 (1982).

Female rats were given 2 hours of access to alcohol (10% v/v and water, 2-bottle choice) daily at the onset of the dark cycle. The rats were maintained on a reverse cycle to facilitate experimenter interactions. The animals were initially assigned to four groups equated for alcohol intakes: Group 1 - vehicle (n =8); Group 2 –positive control (e.g. 5.6 mg/kg AM251; n = 8); Group 3 – low dose test compound (n = 8); and Group 4 – high dose of test compound (n = 8). Test compounds were generally mixed into a vehicle of 30% (w/v) β-cyclodextrin in distilled water at a volume of 1-2 ml/kg. Vehicle injections were given to all groups for the first two days of the experiment. This was followed by 2 days of drug injections (to the appropriate groups) and a final day of vehicle injections. On the drug injection days, drugs were given sc 30 minutes prior to a 2-hour alcohol access period. Alcohol intake for all animals was measured during the test period and a comparison was made between drug and vehicle-treated animals to determine effects of the compounds on alcohol drinking behavior.

Additional drinking studies were done utilizing female C57Bl/6 mice (Charles River). Several studies have shown that this strain of mice will readily consume alcohol with little to no manipulation required (Middaugh et al., "Ethanol Consumption by C57BL/6 Mice: Influence of Gender and Procedural Variables" Alcohol, 17 (3), 175-183, 1999; Le et al., "Alcohol Consumption by C57BL/6, BALA/c, and DBA/2 Mice in a Limited Access Paradigm" Pharmacology Biochemisrty and Behavior, 47, 375-378, 1994).

For our purposes, upon arrival (17-19 g) mice were individually housed and given unlimited access to powdered rat chow, water and a 10 % (w/v) alcohol solution. After 2-3 weeks of unlimited access, water was restricted for 20 hours and alcohol was restricted to only 2 hours access daily. This was done in a manner that the access period was the last 2 hours of the dark part of the light cycle.

Once drinking behavior stabilized, testing commenced. Mice were considered stable when the average alcohol consumption for 3 days was ± 20% of the average for all 3 days. Day 1 of test consisted of all mice receiving vehicle injection (sc or ip). Thirty to 120 minutes post injection access was given to alcohol and water. Alcohol consumption for that day was calculated (g/kg) and groups were assigned (n=7-10) so that all groups had equivocal alcohol intake. On day 2 and 3, mice were injected with vehicle or drug and the same protocol as the previous day was followed. Day 4 was wash out and no injections were given. Data was analyzed using repeated measures ANOVA. Change in water or alcohol consumption was compared back to vehicle for

each day of the test. Positive results would be interpreted as a compound that was able to significantly reduce alcohol consumption while having no effect on water

Oxygen Consumption

Methods:

Whole body oxygen consumption is measured using an indirect calorimeter (Oxymax from Columbus Instruments, Columbus, OH) in male Sprague Dawley rats (if another rat strain or female rats are used, it will be specified). Rats (300-380g body weight) are placed in the calorimeter chambers and the chambers are placed in activity monitors. These studies are done during the light cycle. Prior to the measurement of oxygen consumption, the rats are fed standard chow ad libitum. During the measurement of oxygen consumption, food is not available. Basal pre-dose oxygen consumption and ambulatory activity are measured every 10 minutes for 2.5 to 3 hours. At the end of the basal pre-dosing period, the chambers are opened and the animals are administered a single dose of compound (the usual dose range is 0.001 to 10 mg/kg) by oral gavage (or other route of administration as specified, i.e. s.c., i.p., i.v.). Drugs are prepared in methylcellulose, water or other specified vehicle (examples include PEG400, 30% beta-cyclo dextran and propylene glycol). Oxygen consumption and ambulatory activity are measured every 10 minutes for an additional 1-6 hours post-dosing.

The Oxymax calorimeter software calculates the oxygen consumption (ml/kg/h) based on the flow rate of air through the chambers and difference in oxygen content at inlet and output ports. The activity monitors have 15 infrared light beams spaced one inch apart on each axis, ambulatory activity is recorded when two consecutive beams are broken and the results are recorded as counts.

Resting oxygen consumption, during pre- and post-dosing, is calculated by averaging the 10-min O_2 consumption values, excluding periods of high ambulatory activity (ambulatory activity count > 100) and excluding the first 5 values of the pre-dose period and the first value from the post-dose period. Change in oxygen consumption is reported as percent and is calculated by dividing the post-dosing resting oxygen consumption by the pre-dose oxygen consumption *100. Experiments will typically be done with n = 4-6 rats and results reported are mean +/- SEM.

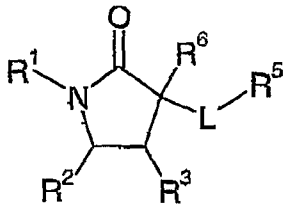
Interpretation:

An increase in oxygen consumption of >10% is considered a positive result. Historically, vehicle-treated rats have no change in oxygen consumption from pre-dose basal.

CLAIMS

What is claimed is:

1. A compound of Formula (I)



(I)

wherein

R^1 and R^2 are each independently a chemical moiety selected from the group consisting of phenyl, pyridinyl, pyrimidinyl, pyrazinyl, 3-6 membered partially or fully saturated heterocycle containing 1 to 3 heteroatoms each independently selected from oxygen, nitrogen or sulfur, and 3-7 membered partially or fully saturated carbocyclic ring, where said moiety is optionally substituted with one or more substituents;

R^3 is hydrogen, (C_1-C_4)alkyl, or a halo-substituted (C_1-C_4)alkyl;

L is a bond, -O-, -O-CH_2-, (C_1-C_3)alkyl, (C_2-C_3)alkenyl, (C_2-C_3)alkynyl, –CH(OH)-, -C(O)-, -C(O)O-, -OC(O)-, -C(O)S-, -NR^4-, -NR^4-((C_1-C_4)alkyl)-, -C(O)NR^4-, or -CH_2-C(O)-NR^4-;

R^4 is hydrogen, or (C_1-C_4)alkyl;

R^5 is a chemical moiety selected from the group consisting of (C_1-C_8)alkyl, phenyl(C_1-C_4)alkyl, phenyl, 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen or sulfur, 3- to 6-membered partially or fully saturated heterocycle containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen or sulfur, partially or fully saturated (C_3-C_7) cycloalkyl, and 5- to 6-membered lactone or lactam, where said moiety is optionally substituted with one or more substituents each independently selected from halo, hydroxy, cyano, nitro, (C_1-C_4)alkyl, partially or fully saturated (C_3-C_7) cycloalkyl, halo-substituted(C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy, halo-substituted(C_1-C_4)alkoxy, γ-butryolactam, γ-butryolactone, -C(O)-R^4, -OC(O)-R^4, -C(O)-O-R^4, -N(R^4)-C(O)-R^4, -C(O)-N(R^4)(R^4), -N(R^4)-C(O)-O-R^4, -O-C(O)-O-R^4, phenylsulfonyl, (C_1-C_4)alkylsulfonyl, benzyl, phenyl, pyridinyl, or pyrimidinyl, where said phenyl is optionally substituted with one to three substituents each independently selected from chloro, fluoro or methyl; and

R^6 is hydrogen, (C_1-C_7)alkyl, phenyl, or phenyl(C_1-C_4)alkyl-, where said phenyl is optionally substituted with one to three substituents each independently selected from fluoro, (C_1-C_4)alkyl, or (C_1-C_4)alkoxy;

a pharmaceutically acceptable salt thereof, a prodrug of the compound or the salt, or a solvate or hydrate of the compound, the salt or the prodrug.

2. The compound of Claim 1 wherein R^1 is phenyl, 2-pyridinyl or 3-pyridinyl, where said phenyl, said 2-pyridinyl and said 3-pyridinyl are optionally substituted with one to three substituents each independently selected from halo, cyano, hydroxyl, $(C_1$-$C_4)$alkyl, $-C(O)-R^4$, halo-subsituted $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkylamino or di$(C_1$-$C_4)$alkylamino; and

R^2 is phenyl optionally substituted with one to three substituents each independently selected from halo, cyano, hydroxyl, $(C_1$-$C_4)$alkyl, $-C(O)-R^4$, halo-subsituted $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkylamino or di$(C_1$-$C_4)$alkylamino;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

3. The compound of Claim 2 wherein L is $-NR^4-$,or $-NR^4-((C_1$-$C_4)$alkyl$)-$; and

R^6 is hydrogen, or $(C_1$-$C_7)$alkyl;

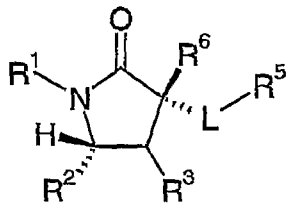
a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

4. The compound of Claim 3 wherein R^5 is $(C_4$-$C_8)$alkyl, cyclohexyl, piperidinyl, piperazinyl, morpholinyl, pyridinyl, or phenyl, where said phenyl is optionally substituted with one or two substituents each independently selected from fluoro, chloro, cyano, nitro, $(C_1$-$C_4)$alkyl, fluoro-substituted$(C_1$-$C_4)$alkyl, hydroxyl$(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkoxy, fluoro-substituted$(C_1$-$C_4)$alkoxy, γ-butryolactam, $-C(O)-OCH_3$, or $-C(O)-NH_2$,

said piperidinyl and said piperazinyl are optionally substituted with phenylsulfonyl, $(C_1$-$C_4)$alkylsulfonyl, benzyl, phenyl, pyridinyl, or pyrimidinyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

5. The compound of Claim 4 wherein said compound of Formula (I) is a compound of Formula (II)



(II)

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

6. The compound of Claim 3 selected from the group consisting of

(3R,5R)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-[(1-methyl-1-phenylethyl)amino]pyrrolidin-2-one;

(3R,5R)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-{[(1R)-1-(4-nitrophenyl)ethyl]amino}pyrrolidin-2-one;

(3R,5R)-1-(4-chlorophenyl)-5-(2,3-dichlorophenyl)-3-[(1-methyl-1-phenylethyl)amino]pyrrolidin-2-one;

(3R,5R)-5-(3-chlorophenyl)-1-(4-chlorophenyl)-3-[(1-methyl-1-phenylethyl)amino]pyrrolidin-2-one;

(3R,5R)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-{[1-(4-fluorophenyl)-1-methylethyl]amino}pyrrolidin-2-one;

4-{(3R,5R)-5-(2-chlorophenyl)-3-[(1-methyl-1-phenylethyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

4-((3R,5R)-5-(2-chlorophenyl)-3-{[1-(4-fluorophenyl)-1-methylethyl]amino}-2-oxopyrrolidin-1-yl)benzonitrile;

4-{(3R,5R)-5-(3-fluorophenyl)-3-[(1-methyl-1-phenylethyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

3-{(2R,4R)-1-(4-cyanophenyl)-4-[(1-methyl-1-phenylethyl)amino]-5-oxopyrrolidin-2-yl}benzonitrile;

4-{(3R,5R)-5-(2-chlorophenyl)-3-[(1-methyl-1-phenylethyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

4-((3R,5R)-5-(2-chlorophenyl)-3-{[1-(4-fluorophenyl)-1-methylethyl]amino}-2-oxopyrrolidin-1-yl)benzonitrile;

4-((3R,5R)-5-(3-fluorophenyl)-3-{[1-(4-fluorophenyl)-1-methylethyl]amino}-2-oxopyrrolidin-1-yl)benzonitrile;

3-((2R,4R)-1-(4-cyanophenyl)-4-{[1-(4-fluorophenyl)-1-methylethyl]amino}-5-oxopyrrolidin-2-yl)benzonitrile;

4-{(3R,5R)-5-(3-chlorophenyl)-3-[(1-methyl-1-phenylethyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

4-{(3R,5R)-5-(3-chlorophenyl)-3-[(3,5-difluorobenzyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

4-[(3R,5R)-5-(3-chlorophenyl)-3-({1-[3-(1-hydroxy-1-methylethyl)phenyl]-1-methylethyl}amino)-2-oxopyrrolidin-1-yl]benzonitrile;

4-{(3R,5R)-5-(3-fluorophenyl)-3-[(1-methyl-1-phenylethyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

4-((3R,5R)-5-(3-fluorophenyl)-3-{[1-(4-fluorophenyl)-1-methylethyl]amino}-2-oxopyrrolidin-1-yl)benzonitrile;

3-{(2R,4R)-1-(4-cyanophenyl)-4-[(1-methyl-1-phenylethyl)amino]-5-oxopyrrolidin-2-yl}benzonitrile;

3-((2R,4R)-1-(4-cyanophenyl)-4-{[1-(4-fluorophenyl)-1-methylethyl]amino}-5-oxopyrrolidin-2-yl)benzonitrile;

3-((2R,4R)-1-(4-chlorophenyl)-4-{[1-(4-fluorophenyl)-1-methylethyl]amino}-5-oxopyrrolidin-2-yl)benzonitrile;

3-[(2R,4R)-1-(4-chlorophenyl)-4-[(1-methyl-1-phenylethyl)amino]-5-oxopyrrolidin-2-yl}benzonitrile;

(3R,5R)-5-(3-chlorophenyl)-1-(5-chloropyridin-2-yl)-3-[(1-methyl-1-phenylethyl)amino]pyrrolidin-2-one;

3-[1-(4-chlorophenyl)-4-({1-methyl-1-[3-(trifluoromethyl)phenyl]ethyl}amino)-5-oxopyrrolidin-2-yl]benzonitrile;

3-(1-(4-chlorophenyl)-4-{[1-(4-fluorophenyl)-1-methylethyl]amino}-5-oxopyrrolidin-2-yl)benzonitrile;

5-(3-chlorophenyl)-1-(5-chloropyridin-2-yl)-3-{[1-(4-fluorophenyl)-1-methylethyl]amino}pyrrolidin-2-one;

(3R,5R)-5-(3-chlorophenyl)-1-(4-chlorophenyl)-3-[(1-methyl-1-phenylethyl)amino]pyrrolidin-2-one;

4-[(3R,5R)-5-(3-fluorophenyl)-3-({1-[3-(1-hydroxy-1-methylethyl)phenyl]-1-methylethyl}amino)-2-oxopyrrolidin-1-yl]benzonitrile;

3-((2S,4S)-1-(4-cyanophenyl)-4-{[1-(4-fluorophenyl)-1-methylethyl]amino}-5-oxopyrrolidin-2-yl)benzonitrile;

4-{(3R,5R)-5-(3-fluorophenyl)-3-[(1-methyl-1-phenylethyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

3-[(2R,4R)-1-(4-cyanophenyl)-4-[(1-methyl-1-phenylethyl)amino]-5-oxopyrrolidin-2-yl}benzonitrile;

4-((3R,5R)-5-(3-fluorophenyl)-3-{[1-(4-fluorophenyl)-1-methylethyl]amino}-2-oxopyrrolidin-1-yl)benzonitrile;

3-[(2R,4R)-1-(4-cyanophenyl)-4-({1-[3-(1-hydroxy-1-methylethyl)phenyl]-1-methylethyl}amino)-5-oxopyrrolidin-2-yl]benzonitrile;

4-{(3R,5R)-5-(3-chlorophenyl)-3-[(1-methyl-1-phenylethyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

4-{(3R,5R)-5-(3-chlorophenyl)-3-[(3,5-difluorobenzyl)amino]-2-oxopyrrolidin-1-yl}benzonitrile;

4-[(3R,5R)-5-(3-chlorophenyl)-3-({1-[3-(1-hydroxy-1-methylethyl)phenyl]-1-methylethyl}amino)-2-oxopyrrolidin-1-yl]benzonitrile;

3-{(2R,4R)-1-(4-chlorophenyl)-4-[(1-methyl-1-phenylethyl)amino]-5-oxopyrrolidin-2-yl}benzonitrile;

(3R,5R)-5-(3-chlorophenyl)-1-(5-chloropyridin-2-yl)-3-[(1-methyl-1-phenylethyl)amino]pyrrolidin-2-one;

(3RS,5RS)-5-(3-bromophenyl)-1-(5-chloropyridin-2-yl)-3-{[1-(4-fluorophenyl)-1-methylethyl]amino}pyrrolidin-2-one;

3-{(2R,4R)-1-(5-chloropyridin-2-yl)-4-[(1-methyl-1-phenylethyl)amino]-5-oxopyrrolidin-2-yl}benzonitrile; and

3-((2R,4R)-1-(5-chloropyridin-2-yl)-4-{[1-(4-fluorophenyl)-1-methylethyl]amino}-5-oxopyrrolidin-2-yl)benzonitrile;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

7. The compound of Claim 2 wherein L is $(C_1\text{-}C_3)$alkyl; and

R^6 is hydrogen, $(C_1\text{-}C_7)$alkyl, or phenyl$(C_1\text{-}C_4)$alkyl-, where said phenyl is optionally substituted with one to three substituents each independently selected from fluoro, $(C_1\text{-}C_4)$alkyl, or $(C_1\text{-}C_4)$alkoxy;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

8. The compound of Claim 7 wherein R^5 is phenyl or a partially or fully saturated cyclohexyl, where said phenyl is optionally substituted with one or two substituents each independently selected from fluoro, chloro, cyano, nitro, $(C_1\text{-}C_4)$alkyl, halo-substituted$(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkoxy, or phenyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

9. The compound of Claim 8 selected from the group consisting of

(3RS,5SR)-3-benzyl-5-(2-chlorophenyl)-1-(4-chlorophenyl)pyrrolidin-2-one;

(3RS,5SR)-3-benzyl-1-(4-chlorophenyl)-5-phenylpyrrolidin-2-one;

4-{[(3RS,5SR)-1-(4-chlorophenyl)-2-oxo-5-phenylpyrrolidin-3-yl]methyl}benzonitrile;

(3RS,5SR)-1-(4-chlorophenyl)-3-(4-nitrobenzyl)-5-phenylpyrrolidin-2-one;

(3RS,5SR)-3-(4-chlorobenzyl)-1-(4-chlorophenyl)-5-phenylpyrrolidin-2-one;

(3RS,5RS)-1,5-bis(4-chlorophenyl)-3-(3,5-difluorobenzyl)pyrrolidin-2-one;

(3RS,5SR)-3-(4-chlorobenzyl)-1,5-bis(4-chlorophenyl)pyrrolidin-2-one;

(3RS,5SR)-1,5-bis(4-chlorophenyl)-3-(4-methylbenzyl)pyrrolidin-2-one;

(3RS,5SR)-3-(4-tert-butylbenzyl)-1,5-bis(4-chlorophenyl)pyrrolidin-2-one;

4-{[(3RS,5SR)-1,5-bis(4-chlorophenyl)-2-oxopyrrolidin-3-yl]methyl}benzonitrile;

(3RS,5SR)-1,5-bis(4-chlorophenyl)-3-(4-nitrobenzyl)pyrrolidin-2-one;

(3RS,5SR)-3-(biphenyl-4-ylmethyl)-1,5-bis(4-chlorophenyl)pyrrolidin-2-one;

(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(4-methylbenzyl)pyrrolidin-2-one;

(3RS,5SR)-3-(3-chlorobenzyl)-1,5-bis(4-chlorophenyl)pyrrolidin-2-one;

(3RS,5RS)-3-(3-chlorobenzyl)-1,5-bis(4-chlorophenyl)pyrrolidin-2-one;

(3RS,5SR)-1,5-bis(4-chlorophenyl)-3-(3-methylbenzyl)pyrrolidin-2-one;
(3RS,5SR)-1,5-bis(4-chlorophenyl)-3-(3-nitrobenzyl)pyrrolidin-2-one;
3-{[(3RS,5SR)-1,5-bis(4-chlorophenyl)-2-oxopyrrolidin-3-yl]methyl}benzonitrile;
(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(3-methylbenzyl)pyrrolidin-2-one;
3-{[(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yl]methyl}benzonitrile;
(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(3-methoxybenzyl)pyrrolidin-2-one;
(3RS,5SR)-3-(3-chlorobenzyl)-5-(2-chlorophenyl)-1-(4-chlorophenyl)pyrrolidin-2-one;
(3RS,5SR)-3-(4-chlorobenzyl)-5-(2-chlorophenyl)-1-(4-chlorophenyl)pyrrolidin-2-one;
(3RS,5SR)-1,5-bis(4-chlorophenyl)-3-(4-methoxybenzyl)pyrrolidin-2-one;
4-{[(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yl]methyl}benzonitrile;
(3RS,5SR)-1,5-bis(4-chlorophenyl)-3-(3-methoxybenzyl)pyrrolidin-2-one;
(3RS,5SR)-1-(4-chlorophenyl)-5-phenyl-3-(2-phenylethyl)pyrrolidin-2-one;
(3RS,5SR)-1-(4-chlorophenyl)-5-phenyl-3-(3-phenylpropyl)pyrrolidin-2-one;
(3RS,5RS)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(cyclohexylmethyl)pyrrolidin-2-one;
4-{[(3S,5R)-1,5-bis(4-chlorophenyl)-2-oxopyrrolidin-3-yl]methyl}benzonitrile;
4-{[(3RS,5RS)-1,5-bis(4-chlorophenyl)-3-methyl-2-oxopyrrolidin-3-yl]methyl}benzonitrile; and
(3RS,5RS)-3-benzyl-1-(4-chlorophenyl)-5-phenylpyrrolidin-2-one;
a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

10. The compound of Claim 2 wherein L is a bond; and
R^6 is hydrogen, or $(C_1$-$C_7)$alkyl;
a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

11. The compound of Claim 10 wherein R^5 is a chemical moiety selected from the group consisting of 5- to 6-membered heteroaryl containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen or sulfur, 5- to 6-membered fully saturated heterocycle containing 1 to 3 heteroatoms independently selected from oxygen, nitrogen or sulfur, where said moiety is optionally substituted with one or more substituents each independently selected from hydroxy, $(C_1$-$C_4)$alkyl, -NHC(O)-$(C_1$-$C_4)$alkoxy, partially or fully saturated $(C_3$-$C_7)$ cycloalkyl, benzyl, phenyl, pyridinyl, or pyrimidinyl;
a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

12. The compound of Claim 11 selected from the group consisting of

(3S,5R)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2-ethyl-1H-imidazol-1-yl)pyrrolidin-2-one;

(3S,5R)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2-propyl-1H-imidazol-1-yl)pyrrolidin-2-one;

(3S,5S)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2-ethyl-1H-imidazol-1-yl)pyrrolidin-2-one;

(3S,5S)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2-propyl-1H-imidazol-1-yl)pyrrolidin-2-one;

(3S,5S)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2-ethyl-4-methyl-1H-imidazol-1-yl)pyrrolidin-2-one;

(3R,5R)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2-isopropyl-1H-imidazol-1-yl)pyrrolidin-2-one; and

(3R,5R)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2-isopropyl-1H-imidazol-1-yl)pyrrolidin-2-one;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

13. The compound of Claim 2 wherein L is –O- or -O-CH_2-; and

R^6 is hydrogen or (C_1-C_7)alkyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

14. The compound of Claim 13 wherein R^5 is a chemical moiety selected from the group consisting of phenyl(C_1-C_4)alkyl and phenyl, where said moiety is optionally substituted with one to three substituents each independently selected from halo, cyano, nitro, (C_1-C_4)alkyl, hydroxy(C_1-C_4)alkyl, (C_1-C_4)alkoxy, -C(O)-R^4, or phenyl;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

15. The compound of Claim 14 selected from the group consisting of

4-{[(3RS,5RS)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yl]oxy}benzonitrile;

(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2,4-difluorophenoxy)pyrrolidin-2-one;

(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(2-fluorophenoxy)pyrrolidin-2-one;

4-{[(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yl]oxy}-2-fluorobenzonitrile;

4-{[(3RS,5SR)-5-(2-chlorophenyl)-1-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl]oxy}benzonitrile;

(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-(4-methylphenoxy)pyrrolidin-2-one;
4-{[(3S,5S)-5-(2-chlorophenyl)-1-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl]oxy}benzonitrile;
4-{[(3R,5R)-5-(2-chlorophenyl)-1-(4-methoxyphenyl)-2-oxopyrrolidin-3-yl]oxy}benzonitrile;
4-{[(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yl]oxy}benzaldehyde;
(3RS,5SR)-3-(benzyloxy)-5-(2-chlorophenyl)-1-(4-chlorophenyl)pyrrolidin-2-one;
4-({[(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yl]oxy}methyl)benzonitrile;
(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-[(3,5-difluorobenzyl)oxy]pyrrolidin-2-one;
(3RS,5SR)-3-[(4-chlorobenzyl)oxy]-5-(2-chlorophenyl)-1-(4-chlorophenyl)pyrrolidin-2-one;
(3RS,5SR)-3-[(3-chlorobenzyl)oxy]-5-(2-chlorophenyl)-1-(4-chlorophenyl)pyrrolidin-2-one;
(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-[(3-methylbenzyl)oxy]pyrrolidin-2-one;
(3RS,5SR)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-3-[(3-nitrobenzyl)oxy]pyrrolidin-2-one;
4-({[(3RS,5SR)-5-(2-chloro-4-fluorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yl]oxy}methyl)benzonitrile
4-((3R,5R)-5-(2-chlorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yloxy)benzonitrile; and
4-(((3S,5S)-5-(2-chloro-4-fluorophenyl)-1-(4-chlorophenyl)-2-oxopyrrolidin-3-yloxy)methyl)benzonitrile;
a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

16. A pharmaceutical composition comprising (1) a compound of any one of the preceding Claims, or a solvate or hydrate of said compound or said salt; and (2) a pharmaceutically acceptable excipient, diluent, or carrier.

17. The composition of Claim 16 further comprising at least one additional pharmaceutical agent.

18. The composition of Claim 17 wherein said additional pharmaceutical agent is a nicotine receptor partial agonist, an opioid antagonist, a dopaminergic agent, an attention deficit disorder agent, an antipsychotic agent, or an anti-obesity agent.

19. A method for treating a disease, condition or disorder which is modulated by a cannabinoid receptor antagonist in animals comprising the step of administering to an animal in need of such treatment a therapeutically effective amount of a compound of Claim 1;

a pharmaceutically acceptable salt thereof, or a solvate or hydrate of said compound or said salt.

20. The method of Claim 19 wherein said compound is administered in combination with a nicotine receptor partial agonist, an opioid antagonist, a dopaminergic agent, an attention deficit disorder agent, an anti-pyschotic agent, or an anti-obesity agent.

21. The method of Claim 19 or 20 wherein said disease, condition or disorder modulated by a cannabinoid receptor antagonist is selected from the group consisting of weight loss, obesity and obesity-related eating disorders, depression, atypical depression, bipolar disorders, psychoses, schizophrenia, behavioral addictions, suppression of reward-related behaviors, alcoholism, tobacco abuse, dementia, seizure disorders, epilepsy, attention deficit disorder, Parkinson's disease, inflammation, gastrointestinal disorders, type II diabetes, and attention or cognitive deficit disorders.

22. The method of Claim 21 wherein said disease, condition or disorder modulated by a cannabinoid receptor antagonist is obesity and obesity-related eating disorders, attention or cognitive deficit disorders, Parkinson's disease, dementia, alcoholism, tobacco abuse and inflammation.

23. A method for treating a disease, condition or disorder modulated by a cannabinoid receptor antagonist in animals comprising the step of administering to an animal in need of such treatment two separate pharmaceutical compositions comprising

(i) a first composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt thereof or a solvate or hydrate of said salt, and a pharmaceutically acceptable excipient, diluent, or carrier, and

(ii) a second composition comprising at least one additional pharmaceutical agent and a pharmaceutically acceptable excipient, diluent, or carrier.

24. The method of Claim 23 wherein said at least one additional pharmaceutical agent is a nicotine partial agonist, an opioid antagonist, a dopaminergic agent, an attention deficit disorder agent, an anti-psychotic agent, or an anti-obesity agent.

25. The method of Claim 23 or 24 wherein said first composition and said second composition are administered simultaneously.

26. The method of Claim 23 or 24 wherein said first composition and said second composition are administered sequentially and in any order.

27. The use of a compound according to any one of Claims 1 through 15 in the manufacture of a medicament for treating a disease, condition or disorder which is modulated by a cannabinoid receptor antagonist.