AZABICYCLIC HETEROCYCLES AS CANNABINOID RECEPTOR MODULATORS

Abstract: The present application describes compounds according to Formula I, pharmaceutical compositions comprising at least one compound according to Formula I and optionally one or more additional therapeutic agents and methods of treatment using the compounds according to Formula I both alone and in combination with one or more additional therapeutic agents. The compounds have the general Formula I, including all prodrugs, pharmaceutically acceptable salts and stereoisomers, R¹, R², R³, R⁴, R⁵, m and n are described herein.
AZABICYCLIC HETEROCYCLES AS CANNABINOID RECEPTOR MODULATORS

RELATED APPLICATION

This application claims priority benefit under Title 35 § 119(e) of United States Provisional Application No. 60/531,451, filed December 19, 2003, the contents of which are herein incorporated by reference.

BACKGROUND OF THE INVENTION

Delta-9-tetrahydrocannabinol or Delta-9 THC, the principle active component of Cannabis sativa (marijuana), is a member of a large family of lipophilic compounds (i.e., cannabinoids) that mediate physiological and psychotropic effects including regulation of appetite, immunosuppression, analgesia, inflammation, emesis, antinociception, sedation, and intraocular pressure. Other members of the cannabinoid family include the endogenous (arachidonic acid-derived) ligands, anandamide, 2-arachidonyl glycerol, and 2-arachidonyl glycerol ether. Cannabinoids work through selective binding to and activation of G-protein coupled cannabinoid receptors. Two types of cannabinoid receptors have been cloned, CB1 (L. A. Matsuda, et al., Nature, 346, 561-564 (1990)), and CB2 (S. Munro, et al., Nature, 365, 61-65 (1993)). The CB1 receptor is highly expressed in the central and peripheral nervous systems (M. Glass, et al., Neuroscience, 77, 299-318 (1997)), while the CB2 receptor is highly expressed in immune tissue, particularly in spleen and tonsils. The CB2 receptor is also expressed on other immune system cells, such as lymphoid cells (S. Galiegue, et al., Eur J Biochem, 232, 54-61 (1995)). Agonist activation of cannabinoid receptors results in inhibition of cAMP accumulation, stimulation of MAP kinase activity, and closure of calcium channels.

There exists substantial evidence that cannabinoids regulate appetitive behavior. Stimulation of CB-1 activity by anandamide or Delta-9 THC results in increased food intake and weight gain in multiple species including humans (Williams and Kirkham, Psychopharm., 143, 315-317 (1999)). Genetic knock-out of CB-1 result in mice that were hypophagic and lean relative to wild-type litter mates (DiMarzo, et al., Nature, 410, 822-825 (2001)). Published studies with CB-1 small molecule
antagonists have demonstrated decreased food intake and body weight in rats (Trillou, et. al., Am. J. Physiol. Regul. Integr. Comp. Physiol., R345-R353, (2003)). Chronic administration of the CB-1 antagonist AM-251 for two weeks resulted in substantial body weight reduction and decreased adipose tissue mass (Hildebrandt, et. al., Eur. J. Pharm, 462, 125-132 (2003)). There are multiple studies that have assessed the anorexic effect of the Sanofi CB-1 antagonist, SR-141716 (Rowland, et. al., Psychopharm., 159-11-116, (2001); Colombo, et. al., Life Sci., 63, 113-117 (1998)). There are at least two CB-1 antagonists in clinical trials for regulation of appetite, Sanofi's SR-141716 and Solvay's SLV-319. Published Phase IIb data reveal that SR-141716 dose-dependently reduced body weight in human subjects over a 16 week trial period. CB-1 antagonists have also been shown to promote cessation of smoking behavior. Phase II clinical data on smoking cessation were presented in September of 2002 at Sanofi-Synthelabo's Information meeting. This data showed that 30.2% of patients treated with the highest dose of SR-141716 stayed abstinent from cigarette smoke relative to 14.8% for placebo.

**DETAILED DESCRIPTION OF THE INVENTION**

The present application describes compounds according to Formula I, pharmaceutical compositions comprising at least one compound according to Formula I and optionally one or more additional therapeutic agents and methods of treatment using the compounds according to Formula I both alone and in combination with one or more additional therapeutic agents. The compounds have the general Formula I

![Chemical Structure]

including all prodrugs, pharmaceutically acceptable salts and stereoisomers, $R^1, R^2, R^3, R^4, R^5, m$ and $n$ are described herein:
DEFINITIONS

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

As used herein, the term "alkyl" denotes branched or unbranched hydrocarbon chains containing 1 to 20 carbons, preferably 1 to 12 carbons, and more preferably 1 to 8 carbons, in the normal chain, such as, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, hexyl, iso-hexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl and the like. Further, alkyl groups, as defined herein, may optionally be substituted on any available carbon atom with one or more functional groups commonly attached to such chains, such as, but not limited to hydroxyl, halo, haloalkyl, mercapto or thio, cyano, alkylthio, cycloalkyl, heteroaracyl, aryl, heteroaryl, carboxyl, carbalkoxy, carboxamido, carbonyl, alkenyl, alkynyl, nitro, amino, alkoxy, aryloxy, arylalkyloxy, heteroaryloxy, amido, -OC(O)NR^5R^9, -OC(O)R^8, -OPO_3H, -OSO_3H, and the like to form alkyl groups such as trifluoromethyl, 3-hydroxyhexyl, 2-carboxypropyl, 2-fluoroethyl, carboxymethyl, cyanobutyl and the like.

Unless otherwise indicated, the term "alkenyl" as used herein by itself or as part of another group refers to straight or branched chains of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 2 to 8 carbons with one or more double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-noneryl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like. Further, alkenyl groups, as defined herein, may optionally be substituted on any available carbon atom with one or more functional groups commonly attached to such chains, such as, but not limited to halo, haloalkyl, alkyl, alkoxy, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxyl, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylethynylamino, nitro, cyano, thiol, alkylthio and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "alkynyl" as used herein by itself or as part of another group refers to straight or branched chains of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons with one or more triple bonds in the normal chain, such as 2-propynyl, 3-butylnyl, 2-butylnyl, 4-pentynyl, 3-
pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynly, 3-undecynyl, 4-dodecynyl and the like. Further, alkynyl groups, as defined herein, may optionally be substituted on any available carbon atom with one or more functional groups commonly attached to such chains, such as, but not limited to halo, haloalkyl, alkyl, alkoxy, alkenyl, aryl, arylalkyl, cycloalkyl, amino, hydroxyl, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, alkylthio and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing one or more double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, appended or fused, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,

Further, any cycloalkyl may be optionally substituted through any available carbon atoms with one or more groups selected from hydrogen, halo, haloalkyl, alkyl, alkoxy, haloalkyloxy, hydroxyl, alkenyl, alkynyl, aryl, aryloxy, heteroaryl, heteroaryloxy, arylalkyl, heteroaryllalkyl, alkanoylamino, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the alkyl substituents.

The term "cycloalkylalkyl" as used herein alone or as part of another group refers to alkyl groups as defined above having a cycloalkyl substituent, wherein said "cycloalkyl" and/or "alkyl" groups may optionally be substituted as defined above.

Unless otherwise indicated, the term "aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-
naphthyl) and may optionally include one to three additional rings fused to a
carbocyclic ring or a heterocyclic ring, for example

Further, "aryl", as defined herein, may optionally be substituted with one or
more functional groups, such as halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl,
alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, heteroaryl,
arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxy carbonyl, aryl carbonyl, arylalkenyl,
aminocarbonylaryl, arylthio, arylsulfonyl, arylazo, heteroarylalkyl, heteroarylalkenyl,
heteroarylheteroaryl, heteroaryl oxo, hydroxyl, nitro, cyano, amino, substituted amino
wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the
other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio,
heteroarylthio, arylthioalkyl, alkoxyarylthio, alkyl carbonyl, aryl carbonyl,
alkylaminocarbonyl, arylaminocarbonyl, alkoxy carbonyl, aminocarbonyl,
alkylcarbonyloxy, aryl carbonyloxy, alkylcarbonylamino, aryl carbonylamino,
aryl sulfonyl, aryl sulfonylalkyl, aryl sulfonylamino or aryl sulfonylaminocarbonyl and/or
any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as
part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2,
3 or 4 hetero atoms such as nitrogen, oxygen or sulfur. Such rings may be fused to an
aryl, cycloalkyl, heteroaryl or heterocyclyl and include possible N-oxides as described
in Katritzky, A. R. and Rees, C. W., eds. Comprehensive Heterocyclic Chemistry: The
Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds 1984, Pergamon
1996, Elsevier Science, Inc., Tarrytown, NY; and references therein. Further, “heteroaryl”, as defined herein, may optionally be substituted with one or more substituents such as the substituents included above in the definition of “substituted alkyl” and “substituted aryl”. Examples of heteroaryl groups include the following:

and the like.

The term "heteroarylalkyl" as used herein alone or as part of another group refers to alkyl groups as defined above having a heteroaryl substituent, wherein said heteroaryl and/or alkyl groups may optionally be substituted as defined above.

The term “heterocyclo”, “heterocycle”, “heterocycl” or “heterocyclic ring”, as used herein, represents an unsubstituted or substituted stable 4 to 7-membered monocyclic ring system which may be saturated or unsaturated, and which consists of carbon atoms, with one to four heteroatoms selected from nitrogen, oxygen or sulfur, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but is not limited to, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperdinyl, oxopyrrolidinyl, oxoazepinyl,

The term "heterocycloalkyl" as used herein alone or as part of another group refers to alkyl groups as defined above having a heterocyclyl substituent, wherein said heterocyclyl and/or alkyl groups may optionally be substituted as defined above.

The terms "arylcycalkyl", "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkyl, alkenyl and alkynyl groups as described above having an aryl substituent. Representative examples of arylicalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, phenethyl, benzhydryl and naphthylmethyl and the like.

The term "alkoxy", "aryloxy", "heteroaryloxy" "arylalkyloxy", or "heteroarylalkyloxy" as employed herein alone or as part of another group includes an alkyl or aryl group as defined above linked through an oxygen atom.

The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine, with bromine, chlorine or fluorine being preferred.

The term "cyano," as used herein, refers to a -CN group.

The term "methylenel," as used herein, refers to a -CH₂- group.

The term "nitro," as used herein, refers to a -NO₂ group.

The compounds of formula I can be present as salts, which are also within the scope of this invention. Pharmacologically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid,
phosphoric acid or a hydrohalic acid, with organic carboxylic acids, such as
alkanecarboxylic acids of 1 to 4 carbon atoms, for example acetic acid, which are
unsubstituted or substituted, for example, by halogen as chloroacetic acid, such as
saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic,
maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for
example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids,
(for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with
organic sulfonic acids, such as (C₁₋₄) alkyl or arylsulfonic acids which are
unsubstituted or substituted, for example by halogen, for example methyl- or p-
toluene- sulfonic acid. Corresponding acid addition salts can also be formed having,
if desired, an additionally present basic center. The compounds of formula I having at
least one acid group (for example COOH) can also form salts with bases. Suitable
salts with bases are, for example, metal salts, such as alkali metal or alkaline earth
metal salts, for example sodium, potassium or magnesium salts, or salts with
ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine,
pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tert-butyl, diethyl,
diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy
lower alkylamine, for example mono, di or triethanolamine. Corresponding internal
salts may furthermore be formed. Salts which are unsuitable for pharmaceutical uses
but which can be employed, for example, for the isolation or purification of free
compounds of formula I or their pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I which contain a basic group
include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate, nitrate or
acetate.

Preferred salts of the compounds of formula I which contain an acid group
include sodium, potassium and magnesium salts and pharmaceutically acceptable
organic amines.

The term “modulator” refers to a chemical compound with capacity to either
enhance (e.g., “agonist” activity) or partially enhance (e.g., “partial agonist” activity)
or inhibit (e.g., “antagonist” activity or “inverse agonist” activity) a functional
property of biological activity or process (e.g., enzyme activity or receptor binding); such
enhancement or inhibition may be contingent on the occurrence of a specific
event, such as activation of a signal transduction pathway, and/or may be manifest only in particular cell types.

The term “bioactive metabolite” as employed herein refers to any functional group contained in a compound of formula I with an open valence for further substitution wherein such substitution can, upon biotransformation, generate a compound of formula I. Examples of such functional groups of bioactive metabolites include, but are not limited to, -OH, -NH or functional groups wherein the hydrogen can be replaced with a functional group such as –PO₃H₂ for example, which, upon biotransformation generates an –OH or –NH functional group of a compound of formula I.

The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates and the like. Prodrug esters may also include, but are not limited to, groups such as phosphate esters, phosphonate esters, phosphonamidate esters, sulfate esters, sulfonate esters, and sulfonamidate esters wherein the ester may be further substituted with groups that confer a pharmaceutical advantage such as-but not limited to-favorable aqueous solubility or in vivo exposure to the bioactive component formula I.

The term “prodrug” as employed herein includes functionalization of bioactive amine- or hydroxyl-containing compounds of formula I to form alkyl-, acyl-, sulfonyl-, phosphoryl-, or carbohydrate-substituted derivatives. Such derivatives are formed by reacting compounds of formula I with alkylating-, acylating-, sulfonylating-, or phosphorylating reagents employing procedures known to those skilled in the art. Alkylation of amines of formula I may result in, but are not limited to, derivatives that include spacer units to other prodrug moieties such as substituted alkoxymethyl-, acyloxymethyl-, phosphoryloxymethyl-, or sulfonyloxymethyl-groups. Alkylation of amines of formula I may result in the generation of quaternary amine salts that act in vivo to provide the bioactive agent (i.e., the compound of formula I).

The term “prodrug” as employed herein includes a precursor to a compound of formula I that, upon bioactivation, can form a bioactive metabolite of formula I.
Examples of such prodrugs can be found in *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) Chapter 1 "Design of Prodrugs: Bioreversible derivatives for various functional groups and chemical entities" pp. 1-92 including subsection 6 "Ring-Opened derivatives as prodrugs for cyclic drugs" pp. 51-55.

Preferred prodrugs consist of a compound of formula I where a pendant hydroxyl is phosphorylated to generate a phosphate derivative. Such a prodrug may also include a spacer group between the compound of formula I and the phosphate group, such as a methyleneoxo-group. Methods to generate such a prodrug from a compound of formula I are known to those skilled in the art, and are listed in the references below.

Preferred prodrugs also consist of a compound of formula I where a pendant amine, such as a pyridine group, is alkylated with a group, such as methyl- or acyloxymethylene-, to form a quarternary ammonium ion salt. Methods to generate such a prodrug from a compound of formula I are known to those skilled in the art, and are listed in the references below.

Any compound that can be converted in vivo to provide the bioactive agent (i.e., the compound of formula I) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art. A comprehensive description of prodrugs and prodrug derivatives are described in:

*The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch. 31, (Academic Press, 1996);

*Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985);


Said references are incorporated herein by reference.

An administration of a therapeutic agent of the invention includes administration of a therapeutically effective amount of the agent of the invention. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat or prevent a condition treatable by administration of a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example, treatment or prevention of the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration.

All stereoisomers of the compounds of the instant invention are contemplated, either in mixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic techniques, chiral HPLC or fractional crystallization.

The compounds of formula I of the invention can be prepared as shown in the following reaction schemes and description thereof, as well as relevant published literature procedures that may be used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.
ABBREVIATIONS

The following abbreviations are employed in the Schemes, Examples and elsewhere herein:

Ac = acetyl
AcOH = acetic acid
Boc = tert-butoxycarbonyl
DCM = dichloromethane
DIPEA = N,N-diisopropylethylamine
DMF = N,N-dimethylformamide
EtOAc = ethyl acetate
Et₃N = triethylamine
Et₂O = diethyl ether
HOBt = 1-hydroxybenzotriazole hydrate
HPLC = high performance liquid chromatography
LAH = lithium aluminum hydride
LC/MS = high performance liquid chromatography and mass spectrometry
MeOH = methanol
MS or Mass Spec = mass spectrometry
NMR = nuclear magnetic resonance spectrometry
PG = protecting group
RT = room temperature
TFA = trifluoroacetic acid
THF = tetrahydrofuran
min = minute(s)
h = hour(s)
L = liter
mL = milliliter
μL = microliter
g = gram(s)
mg = milligram(s)
mol = moles
mmol = millimole(s)
nM = nanomolar

Compounds of the present invention may be prepared by procedures illustrated in the accompanying schemes.

METHODS OF PREPARATION

The compounds of the present invention may be prepared by methods such as those found in the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or can be readily prepared by one of ordinary skill in the art using known methods. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples. Protection and deprotection in the processes below may be carried out by procedures generally known in the art (see, for example, T.W. Greene & P.G.M. Wuts, "Protecting Groups in Organic Synthesis", 3rd Edition, Wiley, 1999). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. and Fleming, I., eds. Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry. 1991, Pergamon Press, New York, NY.; March, J., Advanced Organic Chemistry: Reactions, Mechanisms, and Structure. 4th ed. 1992, New York, NY: John Wiley & Sons; Katritzky, A.R., Meth-Cohn, O. and Rees, C.W., eds. Comprehensive Organic Functional Group Transformations. 1st ed. 1995, Elsevier Science Inc., Tarrytown, NY.; Larock, R.C., Comprehensive Organic Transformations. 1989, New York, NY: VCH Publishers, Inc.; and references therein. Compounds of formula I-XVII can be interconverted to other compounds of formula I-XVII by those skilled in the art or described in the references and examples herein. For all of the schemes and compounds described below, R₁, R₂, R³, R⁴, R⁶, R⁷, R⁸, R⁹ are as described for a compound of formula I.
Compounds of formula I of the present invention can be synthesized from compounds of formula II or III wherein L is hydrogen, halide, or metalloid such as tin, boron and the like by reaction with a metalloid compound such as n-butyllithium, isopropylmagnesium chloride, lithium napthalide, LiTMP and the like as described, for example, in Mongin, F. and Queguiner, G. *Tetrahedron*, 2001, 57(19), 4059-4090; Turck, A. et al. *Tetrahedron*, 2001, 57(21), 4489-4505; to give a compound of formula II where L is a metalloid such as lithium or magnesium and the like, or such metal is exchanged for another metal such as zinc, tin, palladium and the like. Reaction with another group L, R¹-L or R²-L gives compounds of formula II that can be further reacted under similar conditions to give compounds of formula I.

Alternatively, compounds of formula IV where L is oxygen or nitrogen, can be alkylated-, sulfonylated- or acylated using, for example, a base such as K$_2$CO$_3$ and an alkylating agent such as methyliodide or an aldehyde and reducing agent such as acetaldehyde and sodium cyanoborohydride and the like as described, for example, in Abdel-Magid, A. F. et al. J. Org. Chem. 1996, 61 (11), 3849-3862. Or compounds of formula IV where L is oxygen or nitrogen can be reacted with a sulfonylating reagent such as phenylsulfonyl chloride, Cl-S(O)$_n$R$^9$ and the like, or an acylating reagent such as acetyl chloride, methylvchloroformate, and the like, to form compounds of formula I wherein n denotes a double bond and m denotes a single bond.
Compounds of formula V wherein L is a leaving group such as chlorine, fluorine, trifluorosulfonyloxy- and the like can be reacted with an oxygen nucleophile such as the potassium salt of trimethylsilanol, or sodium hydroxide and the like to form compounds of formula I wherein $R^5$ is O and $R^4$ is H or, under basic conditions in the presence of an alkylating agent, such intermediates can be further transformed into compounds of formula I wherein $R^5$ is O and $R^4$ is defined in claim 1. Examples of these transformations can be found herein and in: Nannini, G. et al. *Eur. J. Med. Chem.-Chim. Ther.* 1979, 14 (1), 53-60; Yu et al. *J. Med. Chem.* 2003, 46 (4), 457-460 and references found therein.

Compounds of formula VI can be alkylated with an electrophile such as a substituted benzyl halide, an alkyl halide, an aryl halide, a heteroaryl halide and the like in the presence of a base such as $K_2CO_3$ and solvents such as DMF, THF and the like, optionally catalyzed by palladium, copper and the like to give compounds of formula I. Examples of such transformations can be found herein and in, Edmondson, S. D., Mastracchio, A., Parmee, E. R. *Org. Lett.* 2000, 2 (8), 1109-1112 and references therein.
Compounds of formula VIII wherein \( L \) is a leaving group such as chlorine, fluorine, trifluoromethylsulfonate, and the like, can be reacted with hydrazine in a solvent such as DMF, pyridine, THF and the like to give compounds of formula VII as exemplified herein and in Nannini, G. et al. *Eur. J. Med. Chem.-Chim. Ther.* 1979, 14 (1), 53-60 and references therein. Compounds of formula VII can be reacted with a bis-activated carbonyl such as carbonyl-1,1-dimidazole, phosgene, and the like to give compounds of formula VI.

Compounds of formula X are described wherein \( P \) is defined as a protecting group known to those skilled in the art; many examples of \( P \) can be found in, T.W. Greene & P.G.M. Wuts, "Protecting Groups in Organic Synthesis", 3rd Edition, Wiley, 1999, and methods for installing- and removing such protecting groups are included in said reference and citations therein. When \( P \) resides on oxygen, then \( k \) is single bond and \( l \) is double bond; alternatively, when \( P \) resides on nitrogen, then \( k \) is double bond and \( l \) is single bond. The protecting group, \( P \), in compounds of formula X can be removed to give compounds of formula IX that are further converted to compounds of formula VIII wherein \( L \) is a leaving group such as fluorine, chlorine, trifluoromethylsulfonate and the like. For example, the conversion of a compound of formula X wherein \( P \) is an optionally substituted benzyl-group occurs with \( \text{AlCl}_3 \) in
toluene to give a compound of formula IX. In the course of these transformations, $R^4$, $R^5$, $n$ and $m$ may be interconverted to other groups selected from the definitions of $R^4$, $R^5$, $n$ and $m$. Examples of similar methods can be found herein and in Nannini, G. et al. *Eur. J. Med. Chem.-Chim. Ther.* 1979, *14* (1), 53-60 and references therein.

Compounds of formula IX can be reacted with POCl$_3$ to give compounds of formula VIII wherein $L$ is chlorine. Examples of similar transformations can be found herein and in, Yu et al. *J. Med. Chem.* 2003, *46* (4), 457-460 and references therein.

**SCHEME VII**

Compounds of formula XII wherein $L$ is a leaving group such as chlorine, bromine and the like, and $P$ is defined in the discription of scheme VI, can be converted into compounds of formula XI by reaction of $R^1$-$M$ or $R^2$-$M$ optionally catalyzed by a transition metal such as palladium, copper and the like. $M$ is defined as a metalloid such as tin, boron, sodium, lithium and the like or $M$ can be an activated hydrogen that is lost upon coupling to compounds of formula XII or XI. Compounds of formula XI can be reacted with $R^1$-$M$ or $R^2$-$M$ optionally catalyzed by a transition metal such as palladium, copper and the like to give compounds of formula X.

Synthesis, 1981(12), 974-975; and references therein.

SCHEME VIII

Compounds of formula XVI wherein L is an activated group such as chlorine,
bromine and the like and Z is O or N are commercially available, or can be
synthesized by those skilled in the art. Reaction of compounds of formula XVI with
a compound of formula XV, hydrazine for example (where R^4 is hydrogen), in a
solvent such as DMF, water or THF, or in the absence of cosolvent gives a compound
of formula XIV. Examples of such transformations can be found herein and in:
1071-1077. A compound of formula XIV wherein R^4 is hydrogen can be converted to
a compound of formula XIII with base, such as K_2CO_3 in solvents such as DMF, THF
and the like. A compound of formula XIII can be further transformed with base, such
as K_2CO_3 in solvents such as DMF, THF and the like to give compounds of formula
XII wherein P is defined in the discussion of scheme VI.

SCHEME IX

Compounds of formula I that contain a bioactive metabolite, as defined above,
can be converted to a prodrug of formula XVII by methods known to those skilled in
the art, including methods described or referenced in the citations above. Examples of
such transformations include, but are not limited to, transformation of an –OH group to a phosphate by methods known to those skilled in the art, and described in Haftendorn, R., Ulbrich-Hoffmann, R. *Tetrahedron* 1995, 51 (4), 1177-1186, *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and references therein.

Compounds of formula I that contain an –NH group can be sulfated as described in Tschamber, T., Streith, J. *Heterocycles* 1990, 30 (1), 551-559. Compounds of formula I that contain a nitrogen can be reacted with an alkylating agent such as chloromethylacetate and the like to give a prodrug that, upon biotransformation, can release compounds of formula I.

Standard protecting groups may be used at any stage of the synthesis, for example in manipulating a functional group to convert one compound of formula I to another compound of formula I.

Parallel synthesis may be employed in the preparation of compounds, for example, where the intermediates possess an activated reaction center: such as but not limited to, the nitrogen of the triazolone, the nitrogen of the pyridazinone, a reactive heteroaryl chloride for Suzuki coupling chemistry or a carboxylic acid for amide coupling chemistry.
EXAMPLES

The following Examples serve to better illustrate, but not limit, some of the preferred embodiments of the invention.

Analytical HPLC Methods Employed in Characterization of Examples

Analytical HPLC/MS was performed on Shimadzu LC10AS liquid chromatographs and Waters ZMD Mass Spectrometers using the following methods:

Unless otherwise indicated, Method A is used in the characterization of intermediates or final compounds of the examples listed in the experimentals or in the tables.

Method A. Linear gradient of 0 to 100% solvent B over 4 min, with 1 min hold at 100% B;
UV visualization at 220 nm
Column: Phenomenex Luna C18 4.6 x 50 mm
Flow rate: 4 ml/min
Solvent A: 0.2% phosphoric acid, 90% water, 10% methanol
Solvent B: 0.2% phosphoric acid, 90% methanol, 10% water

EXAMPLE 1

Preparation of 7,8-Bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione
EXAMPLE 1A

Preparation of 4,5-Dichloro-1,2-dihydropyridazine-3,6-dione

To a round bottom flask was added water (170 ml) and hydrazine dihydrochloride salt (41.9 gm, 398.8 mmol). The solution was brought to reflux and dichloromandelic anhydride (66.6 gm, 398.9 mmol) was added portionwise. The reaction was stirred at reflux for 30 min. After this time, the solution was cooled to RT and the solid was collected by filtration to give the title compound, 4,5-dichloro-1,2-dihydropyridazine-3,6-dione (65 gm, 90% yield) as white solid. MS(M+1)=181.0

EXAMPLE 1B

Preparation of 2-Benzyl-6-(benzyl oxy)-4,5-dichloropyridazin-3(2H)-one

To a r.b. flask was added 4,5-dichloro-1,2-dihydropyridazine-3,6-dione (20 gm, 73.8 mmol), DMF (200 ml), potassium carbonate (20.36 gm, 147.6 mmol) and benzylbromide (15.14 gm, 88.56 mmol). The reaction was stirred at 50°C for 6 hrs and then stirred at RT overnight. After this time, the reaction was poured into a 1:1 water: hexane mixture (2000mL). The resultant mixture was stirred at r.t for 1 h. A solid precipitate formed and the precipitate was collected by filtration to give the title compound, 2-benzyl-6-(benzyl oxy)-4,5-dichloropyridazin-3(2H)-one (23.9 gm, 90% yield) as light yellow solid. $^1$H(DMSO-D6) 7.45(m, 2H), 7.35(m, 4H), 7.30(m, 4H), 5.26(s, 2H), 5.17(s, 2H)
EXAMPLE 1C
Preparation of 2-Benzyl-6-(benzyloxy)-4,5-bis(4-chlorophenyl)pyridazin-3(2H)-one

To a round bottom flask was added 2-benzyl-6-(benzyloxy)-4,5-dichloropyridazin-3(2H)-one (20gm, 55.4mmol), 4-chlorophenylboronic acid (19.07 gm, 121.88 mmol), 2N sodium carbonate(124.7 ml, 249.3 mmol), toluene(200 ml) and Pd(PPh₃)₄ (3.2 gm, 2.77mmol). The reaction was stirred at 100°C for 36 hours. After this time, the solution was cooled to r.t and the organic layer was separated. The organic layer was washed with water (100 ml), saturated aqueous NaCl (100 ml). The organic layer was dried(MgSO₄), filtered and concentrated. The crude material was recrystallized from methanol (150 ml) at -25°C. The solid was collected by filtration to give the title compound, 2-benzyl-6-(benzyloxy)-4,5-bis(4-chlorophenyl)pyridazin-3(2H)-one, (19.5 gm, 70% yield) as light yellow solid. MS (M+H) = 513.1.

EXAMPLE 1D
Preparation of 4,5-Bis(4-chlorophenyl)-1,2-dihydropyridazine-3,6-dione

To a round bottom flask was added 2-benzyl-6-(benzyloxy)-4,5-bis(4-chlorophenyl)pyridazin-3(2H)-one (15.5 gm, 30.21 mmol), toluene(70 ml) and alumina chloride (10.08 gm, 75.54 mmol). The reaction was stirred at 90°C for 2 h. After this time, the reaction was cooled to 0°C and water (200 ml) was slowly added to the reaction. The solution was extracted with ethyl acetate (3 L). The organic layer
was washed with water (200 ml) and saturated aqueous NaCl (200 ml). The organic layer was dried (MgSO₄), filtered and concentrated. The title compound, 4,5-bis(4-chlorophenyl)-1,2-dihydropyridazine-3,6-dione, was obtained as a solid and used in the without further purification. MS (M+H) = 330.9, 333.0

**EXAMPLE 1D**

Preparation of 3,6-Dichloro-4,5-bis(4-chlorophenyl)pyridazine.

![Chemical structure](image)

To the 4,5-bis(4-chlorophenyl)-1,2-dihydropyridazine-3,6-dione was added POCl₃ (50 ml), dropwise. The resultant reaction mixture was heated reflux for 2 h. The reaction turned into black. After this time, POCl₃ was removed under reduced pressure. To the residue was slowly added ice (250 gm) followed by the slow addition of water (250 ml). A solid precipitate was formed which was then collected by filtration to give product as dark solid. The crude product was dissolved in CH₂Cl₂ (250 ml) and the solution was filtered through Celite(30 ml). Collect the filtrate and concentrate to give brown solid. The crude solid was recrystallized from CH₂Cl₂ (30 ml) and hexanes (500 mL) to give the title compound, 3,5-dichloro-4,5-bis(4-chlorophenyl)pyridazine as beige solid (5.0 gm, 45% for the 2 steps). MS; (M+H) = 368.5, 370.5

**EXAMPLE 1E**

Preparation of 1-(6-Chloro-4,5-bis(4-chlorophenyl)pyridazin-3-yl)hydrazine

![Chemical structure](image)

To a r.b. flask was added 3,5-dichloro-4,5-bis(4-chlorophenyl)pyridazine (4.5 gm, 12.2 mmol), pyridine (20 ml) and hydrazine monohydrate (1.494 gm, 30.49...
mmol). The reaction mixture was stirred at 120°C for 1 h. After this time, the reaction mixture was cooled to RT. Water (400 ml) was then added and a solid precipitated. The solution was filtered and the solid was collected and air dried overnight to give the title compound, 1-(6-chloro-4,5-bis(4-chlorophenyl)pyridazin-3-yl)hydrazine (3.7 gm, 83% yield) as a solid. MS (M+H)=364.9

**EXAMPLE 1F**

**Preparation of 6-Chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one**

![Chemical Structure](image)

To a r.b. flask was added THF (50 ml) and carbonyldiimidazole (CDI) (8.11 gm, 50 mmol). After the CDI was completely dissolved, 1-(6-chloro-4,5-bis(4-chlorophenyl)pyridazin-3-yl)hydrazine (3.65 gm, 10 mmol) was added in 4 portions over 10 min. The reaction was stirred at RT for 2 h. After this time, the reaction was poured into water (300 ml). The solution was filtered to give product 6-chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one to give the title compound 6-chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (3.6 gm, 92% yield) as a solid. MS (M+H) = 390.9, 392.9; ¹H NMR (DMSO-D6) 7.39-7.44 (m, 4H), 7.28 (m, 4H).
EXAMPLE 1G

Preparation of 6-Chloro-7,8-bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one

To a r.b. flask was added 6-chloro-7,8-bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (1200 mg, 3.077 mmol), DMF (10 ml), potassium carbonate (0.64 gm, 4.62 mmol), and iodomethane (0.89 gm, 6.15 mmol). The reaction was stirred at RT for 4 h. After this time, water (200 ml) was added to the reaction and a solid precipitated. The solid was collected by filtration to give the title compound, 6-chloro-7,8-bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (1.1 gm, 89% yield). MS (M+H)=404.9, 406.9; \[^1^H\text{NMR}(\text{DMSO}-\text{D}6)\ 7.42(m, 4H), 7.28(m, 4H), 3.56(s, 3H). \[^{13}C\text{NMR} (\text{DMSO}-\text{D}6)\ 147.95, 147.08, 136.18, 135.51, 133.95, 133.37, 131.85, 131.65, 131.20, 128.86, 128.09, 128.01, 32.95.\]

EXAMPLE 1H

Preparation of 7,8-Bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

To a round bottom flask was added 7,8-bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (1.2 gm, 3.29 mmol), THF (15 ml), and potassium trimethylsilanolate (1.7gm, 13.2 mmol). The reaction was refluxed for 2 hrs. The reaction was then cooled to RT, and the solution was concentrated under reduced pressure. The residue was treated with water (20 ml) and the pH was
adjusted to 5 using 1N HCl. To the resultant solution was added ethyl acetate (15 ml) and hexanes (15 ml) and the solution was stirred for 5 min. A precipitate was collected by filtration to give the title compound, 7,8-bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (1.2 gm, 95% yield) as yellow solid. MS (M+H)=386.9 ¹H NMR (DMSO-D6) 12.60(s, 1H), 7.34(d, 2H), 7.29(d, 2H), 7.23(d, 2H), 7.15(d, 2H), 3.46(s, 3H).

**EXAMPLE 2**

**Preparation of 7,8-Bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione**

To a r.b. flask was added 6-chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (100 mg, 0.256 mmol), prepared as described in Example 1F, THF (5 ml) and potassium trimethylsilylanolate (132 mg, 1.026 mmol). The reaction mixture was stirred at 85°C for 1.5 hrs. After this time, the solution was cooled to RT and the reaction was diluted with water (25 ml). The pH of the solution was adjusted to 4 with 1N HCl. The resultant solution was extracted with EtOAc (3 x 20 ml). The combined organic layers were washed with water (20 ml), saturated NaCl (20 ml). The organic layers was dried (MgSO₄), filtered and concentrated to give the title compound, 7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (90 mg, 95% yield) as yellow solid. MS (M+H)=372.9
EXAMPLE 3
Preparation of 2-(4-(Trifluoromethyl)benzyl)-6-chloro-7,8-bis(4-chlorophenyl)-
[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one

To a solution of 6-chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-
b]pyridazin-3(2H)-one, (750 mg, 1.92 mmol), prepared as described in Example 1F,
in DMF (10 mL) was added K₂CO₃ (270 mg, 1.95 mmol) and 4-(trifluoromethyl)benzyl bromide (460 mg, 1.92 mmol). The reaction mixture was stirred at 75°C for 1 h under Argon. It was cooled to RT diluted with water (50 mL) and the solid was collected by filtration. The solid was washed with water (25 mL x 2) and dried in a vacuum oven at 50°C overnight to give the title compound, 2-(4-(trifluoromethyl)benzyl)-6-chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one, (990 mg, 94%) as yellow powder. HPLC: 4.23 min; MS: M+H = 549.

EXAMPLE 4
Preparation of 2-(4-(Trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-6-
(methylamino)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one

A mixture of 2-(4-(trifluoromethyl)benzyl)-6-chloro-7,8-bis(4-chlorophenyl)-
[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (50 mg, 0.091 mmol), prepared as described in Example 3, and 2.0 M methyl amine in THF (0.4 mL) was stirred at reflux for 12 h. After this time, the reaction mixture was cooled to RT and diluted with water (5 mL). The resultant solution was extracted with EtOAc (5 mL x 3). The
combined organic layers were washed with water (5 mL x 2) followed by saturated aqueous NaCl (5 mL x 2). The organic layer was dried over MgSO₄, filtered and concentrated to obtain a crude product. The crude product was purified by preparative reverse phase HPLC to give the title compound, 2-(4-(trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-6-(methylamino)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (31.5 mg, 64%) as pale yellow solid. HPLC : 4.17 min; MS: M+H = 544; ¹H NMR (CDCl₃), ppm: 7.55 (2H, d, J=10.0 Hz), 7.47 (2H, d, J=10.0 Hz), 7.34 (2H, d, J=10.0 Hz), 7.21 (2H, d, J=10.0 Hz), 7.09 (2H, d, J=10.0 Hz), 7.05 (2H, d, J=10.0 Hz), 5.18 (2H, s), 4.19-4.21 (1H, br), 2.95 (3H, d, J=5.0 Hz).

EXAMPLE 5

Preparation of 7,8-Bis(4-chlorophenyl)-2-methyl-5-((5-(trifluoromethyl)pyridin-2-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

![Chemical Structure](image)

EXAMPLE 5A

Preparation of 2-(Chloromethyl)-5-(trifluoromethyl)pyridine

![Chemical Structure](image)

The mixture of 5-(trifluoromethyl)pyridin-2-yl)methanol HCl salt (293mg, 1.4mmol) and SOCl₂(1.5ml) was stirred for 10 min. After this time, the solution was concentrated under reduced pressure to give the title compound, 2-(chloromethyl)-5-(trifluoromethyl)pyridine HCl salt.
EXAMPLE 5B

Preparation of 7,8-Bis(4-chlorophenyl)-2-methyl-5-((5-(trifluoromethyl)pyridin-2-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

The solution of 8-bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (430mg, 1.11mmol), prepared as described in example 1, 2-(chloromethyl)-5-(trifluoromethyl)pyridine (1.4mmol), K₂CO₃ (620mg, 4.5mmol) in DMF (10ml), was heated at 80°C for 1 h. After this time, the solution was cool to RT and diluted with ethyl acetate. The resulting solution was then washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified using silica gel column chromatography using an automated system eluting with a gradient (20-50% Ethyl acetate-Hexane) to give the title compound, 7,8-bis(4-chlorophenyl)-2-methyl-5-((5-(trifluoromethyl)pyridin-2-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (110mg, 18%) as light yellow solid. In addition, the O-allylated product, 7,8-bis(4-chlorophenyl)-2-methyl-6-((5-(trifluoromethyl)pyridin-2-yl)methoxy)-5,6-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one was obtained from the HPLC separation of the crude product. 7,8-Bis(4-chlorophenyl)-2-methyl-5-((5-(trifluoromethyl)pyridin-2-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione: MS, M+H=546; ¹H NMR (CDCl₃) δ 8.75(1H), 7.90(1H), 7.49(1H), 7.29(2H), 7.22-7.18(4H), 7.10(2H), 6.15(2H), 3.53(3H).
EXAMPLE 6

Preparation of 7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

EXAMPLE 6A

Preparation of 6-chloro-7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one

To a solution of 6-chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (0.43g, 1.1mmol), prepared as described in example 1F, in DMF (8ml) at 0°C was added NaH (57mg, 1.4mmol). After 15 min, 2-trimethylsilylethoxymethyl chloride (0.25ml, 1.4mmol) was added. The reaction was stirred for 0.5 h at RT. After this time, water was added. The resulting solution was extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography using an automated system eluting with a gradient of (Ethyl acetate-Hexanes) to give the title compound, 6-chloro-7,8-bis(4-chlorophenyl)-2-((2-(2-(trimethylsilyl)ethoxy)ethoxy)methyl)[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one as a yellow foam (0.48g, 84%).
EXAMPLE 6B

Preparation of 7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

To the solution of 6-chloro-7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one, (0.48g, 0.92mmol) in THF (20ml) was added potassium trimethylsilylazole (TMSOK) (0.25g, 1.95mmol). The solution was heated to reflux. After 0.5 h, the solution was cooled to RT and 1N HCl solution was added until the reaction was acidic. The resulting solution was extracted with ethyl acetate. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using an automated system to give the title compound, 7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione, (260mg, 56%) as a yellow solid.

EXAMPLE 7

Preparation of 5-(4-(trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione
EXAMPLE 7A
Preparation of 5-(4-(trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-2-((2-
(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

The solution of 7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-
[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione, (112mg, 0.22mmol), prepared as
described in example 6B, 4-(trifluoromethyl)benzyl bromide (58mg, 0.24mmol),
K₂CO₃ (91mg, 0.66mmol) in DMF (2ml), was heated at 80°C for 0.75 hour. After this
time, the solution was cooled to RT and diluted with ethyl acetate. The resulting
solution was washed with water. The organic layer was dried over Na₂SO₄, filtered
and concentrated under reduced pressure to give the title compound, 5-(4-
(trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-
[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione, (160mg).

EXAMPLE 7B
Preparation of 5-(4-(Trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-
[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

The solution of 5-(4-(trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-2-((2-
(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione
(118mg, 0.18mmol) in 4M HCl in dioxane (4ml) in a sealed tube was heated at 90°C
for 6 hours. After this time, the reaction mixture was cooled to RT, and subsequently concentrated under reduced pressure. The resulting crude product was purified by reverse phase HPLC to give the title compound, the final product, 5-((trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione, as colorless foam (60mg, 66%). MS M+H=531; 1H (CDCl3) d 11.46(1H), 7.70(2H), 7.55(2H), 7.27(4H), 7.14(2H), 7.06(2H), 5.96(2H).

EXAMPLE 8
Preparation of 6-Chloro-7-(4-chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one and 6-Chloro-8-(4-chlorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one

EXAMPLE 8A
Preparation of 2-Benzyl-6-(benzylxyloxy)-5-chloro-4-(4-chlorophenyl)pyridazin-3(2H)-one and 2-Benzyl-6-(benzylxyloxy)-4-chloro-5-(4-chlorophenyl)pyridazin-3(2H)-one

To a solution of 2-benzyl-6-(benzylxyloxy)-4,5-dichloropyridazin-3(2H)-one(11.8g, 32.7mmol), prepared as described in example 1B, in toluene (200ml) was added Pd(PPh₃)₄ (2.26g, 1.96mmol). After 5min, 2N aqueous sodium carbonate (65 ml, 130mmol) solution was added, followed by 4-chlorophenylboronic acid (7.16g, 45.8 mmol). The reaction was stirred at 100°C for 6 h. After this time, the solution
was cooled RT and the reaction mixture was diluted with ethyl acetate. The resultant solution was washed with water, saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude products were purified using silica gel column chromatography eluting with a gradient of 10-20% Ethyl acetate/Hexane to give the title compounds, 2-benzyl-6-(benzylxy)-5-chloro-4-(4-chlorophenyl)pyridazin-3(2H)-one and 2-benzyl-6-(benzylxy)-4-chloro-5-(4-chlorophenyl)pyridazin-3(2H)-one which were obtained as a mixture.

EXAMPLE 8B

Preparation of 2-Benzyl-6-(benzylxy)-4-(4-chlorophenyl)-5-(pyridin-4-yl)pyridazin-3(2H)-one and 2-Benzyl-6-(benzylxy)-5-(4-chlorophenyl)-4-(pyridin-4-yl)pyridazin-3(2H)-one

\[
\begin{align*}
\text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{N}
\end{align*}
\]

To a solution the mixture of 2-benzyl-6-(benzylxy)-5-chloro-4-(4-chlorophenyl)pyridazin-3(2H)-one and 2-benzyl-6-(benzylxy)-4-chloro-5-(4-chlorophenyl)pyridazin-3(2H)-one (9.9g, 22.7mmol), prepared as described in Example 8A, in toluene (136ml) was added Pd(PPh₃)₄ (2.35g, 1.17mmol). After 2min, 2N sodium carbonate (45.4 ml, 90.8mmol) solution was added, followed by 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (8.5g, 41.4 mmol). The reaction was stirred at 100°C for 42 hours. After this time, the reaction mixture was cooled to RT and diluted with ethyl acetate. The resulting solution was washed with water and saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by silica gel column chromatography using an automated system and eluting with a gradient of 20-50% Ethyl acetate-Hexane to give the title compounds 2-benzyl-6-(benzylxy)-4-(4-chlorophenyl)-5-(pyridin-4-yl)pyridazin-3(2H)-one and 2-benzyl-6-(benzylxy)-5-(4-
chlorophenyl)-4-(pyridin-4-yl)pyridazin-3(2H)-one as a mixture, as light yellow solid (4.5g, 29% two steps).

EXAMPLE 8C

Preparation of 4-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,2-dihydropyridazine-3,6-dione

To a solution of 2-benzyl-6-(benzyloxy)-4-(4-chlorophenyl)-5-(pyridin-4-yl)pyridazin-3(2H)-one and 2-benzyl-6-(benzyloxy)-5-(4-chlorophenyl)-4-(pyridin-4-yl)pyridazin-3(2H)-one (2.8g, 5.8mmol) in toluene (35ml) was added AlCl₃ (3.1g, 23.2mmol). After stirring at 80°C for 30 min. After this time, the reaction mixture was cooled to RT and 40ml water was added. A precipitate formed which was subsequently collected by filtration. The title compound, 4-(4-chlorophenyl)-5-(pyridin-4-yl)-1,2-dihydropyridazine-3,6-dione was obtained as a yellow powder (1.1g, 63%).

EXAMPLE 8D

Preparation of 3,6-Dichloro-4-(4-chlorophenyl)-5-(pyridin-4-yl)pyridazine

A sealed tube with of 4-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,2-dihydropyridazine-3,6-dione (0.1g, 0.33mmol) and POCl₃ (0.3ml, 3.2mmol) was stirred at 135°C in an oil bath for 1h. After this time, the solution was cooled to RT and poured into 1.5N NaOH-ice water (9.3ml, 14mmol). Ethyl acetate was added to the resultant solution. The organic layer was washed with saturated aqueous NaCl. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced
pressure to give the title compound, 3,6-Dichloro-4-(4-chlorophenyl)-5-(pyridin-4-yl)pyridazine a brown foam (90mg) which was used without further purification.

**EXAMPLE 8E**

**Preparation of 6-Chloro-7-(4-chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one and 6-Chloro-8-(4-chlorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one**

To a solution of 3,6-dichloro-4-(4-chlorophenyl)-5-(pyridin-4-yl)pyridazine (0.69g, 2.1mmol) in ethanol (10ml) was added hydrazine monohydrate (1.2ml, 24.7mmol). The reaction was stirred at 80°C for 1h. After this time, the reaction mixture was concentrated under reduced pressure. The crude product was then suspended in THF and CDI (1.36g, 8.4mmol) was added. The reaction turned to brownish clear solution, then to a suspension again. After stirring for 20 min, ethyl acetate was added. The resulting solution was washed with water and saturated NaCl. The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography eluting with a gradient of 5%-10% methanol-dichloromethane to give 6-chloro-7-(4-chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one as a brown solid (0.52g) and 6-chloro-8-(4-chlorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one as light brown solid (0.27g).
EXAMPLE 9

Preparation of 7-(4-Chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

To the solution of 6-chloro-7-(4-chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (28mg, 0.078mmol), prepared as described in Example 8B, in THF (3ml) was added potassium trimethylsilyl oxide, TMSOK, (36mg, 0.28mmol). The reaction mixture was refluxed for 1 hour. After this time, the solution was cooled to RT. The solution was concentrated under reduced pressure. The resulting crude product was purified by reverse phase HPLC to give the title compound, 7-(4-chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione, (8mg, 22%) as a yellow solid.

EXAMPLE 10

Preparation of 8-(4-chlorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione

To the solution of 6-Chloro-8-(4-chlorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (29mg, 0.081mmol), prepared as described in Example 9, in THF (3ml) was added potassium trimethylsilyl oxide, TMSOK, (36mg, 0.28mmol). The solution was heated to refluxed for 15 min. After this time, the solution was cooled to RT. The reaction mixture was concentrated under reduced pressure. The crude material was purified by reverse phase HPLC to give the title compound, 8-(4-chlorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione, (12mg, 32%) as a yellow solid.
EXAMPLE 11

Preparation of 4-((7-(4-Chlorophenyl)-2-methyl-3,6-dioxo-8-(pyridin-4-yl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-5(6H)-yl)methyl)benzonitrile

The solution of 7-(4-chlorophenyl)-2-methyl-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (10mg, 0.028mmol), 4-(bromomethyl)benzonitrile (7mg, 0.036mmol), K₂CO₃ (12mg, 0.084mmol) in DMF (0.5ml), was heated at 80°C for 20 min. After this time, the reaction mixture was cooled to RT and diluted with ethyl acetate. The resulting solution was then washed with water. The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC to give the title compound, 4-((7-(4-chlorophenyl)-2-methyl-3,6-dioxo-8-(pyridin-4-yl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-5(6H)-yl)methyl)benzonitrile (6.5mg, 40%) as the mono trifluoro acetate salt as a yellow solid. Rt=2.78, M+H=469; ¹H NMR (CD3OD) δ 8.81(2H), 7.71-7.60(6H), 7.32(2H), 7.07(2H), 5.96(2H), 3.57(3H).

EXAMPLE 12

Preparation of 4-((7-(4-Chlorophenyl)-3,6-dioxo-8-(pyridin-4-yl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-5(6H)-yl)methyl)benzonitrile
To the solution of 7-(4-chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (8mg, 0.023mmol), prepared as described in Example 9 in DMF (0.3ml) was added K$_2$CO$_3$ (5mg, 0.036mmol) followed by 4-(bromomethyl)benzonitrile (5mg, 0.025mmol). After 15min, the reaction mixture was diluted with ethyl acetate. The resultant solution was then washed with water. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC to give the title compound, 4-((7-(4-chlorophenyl)-3,6-dioxo-8-(pyridin-4-yl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyrazin-5(6H)-yl)methyl)benzonitrile, (4.2mg, 32%) as a mono trifluoroacetate salt as a yellow foam. MS M+H=454; $^1$H (CD3OD) δ 8.68(2H), 7.71-7.65(6H), 7.28(2H), 7.20(2H), 5.94(2H).

EXAMPLE 13
Preparation of 4-((8-(4-Chlorophenyl)-3,6-dioxo-7-(pyridin-4-yl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyrazin-5(6H)-yl)methyl)benzonitrile

![Chemical structure](image)

To the solution of 7-(4-chlorophenyl)-2-methyl-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (12mg, 0.034mmol), prepared as described in Example in DMF (0.5ml) was added K$_2$CO$_3$ (7mg, 0.05mmol) followed by 4-(bromomethyl)benzonitrile (8mg, 0.041mmol). After 15min, the reaction mixture was diluted with ethyl acetate. The resultant solution was washed with water. The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC to give the title compound, 4-((8-(4-chlorophenyl)-3,6-dioxo-7-(pyridin-4-yl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyrazin-5(6H)-yl)methyl)benzonitrile, (3.5mg, 18%) as a mono
trifluoroacetate salt as a yellow foam. MS M+H=455. $^1$H (CD$_3$OD) $\delta$ 8.66(2H), 7.71-7.65(6H), 7.34-7.31(4H), 5.93(2H).

**EXAMPLES 14 TO 48**

The following Examples were prepared according to methods and procedures above:

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The compounds of Set A below, in which R¹ varies, R² is 4-chlorophenyl, R³ is 2-(trifluoromethyl)pyridin-5-ylmethyl, R⁴ is methyl, R⁵ is O, n is single bond and m
is double bond, may be prepared by one skilled in the art by the methods described
above. Furthermore, the variations of R\textsuperscript{1} demonstrated herein can be combined with
R\textsuperscript{2}-R\textsuperscript{9}, n and m found in the working examples above. The compounds of Set A are
meant to further illustrate the scope of the invention without being limiting in any
way.

**Set A:**

![Chemical structures](image-url)
As noted above, Set A consists of compounds that differ from one another only in the identity of $R^1$ with $R^2$ fixed as 4-chlorophenyl. Set A may be considered a one dimensional library of example compounds. Were one to vary both $R^1$ and $R^2$, a two dimensional library of example compounds would result. Set B is the two dimensional library that consists of all permutations of all of the variants of $R^1$ represented in Set A, the working examples, and a set of $R^2$ variants listed below. In Set B, $R^3$ is 2-(trifluoromethyl)pyridin-5-ylmethyl, $R^4$ is methyl, $R^5$ is O, $n$ is single bond and $m$ is double bond. The compounds of Set B may be prepared by one skilled in the art by the methods described above. The compounds of Set B are meant to further illustrate the scope of the invention without being limiting in any way.
$R^2$ variants of Set B:
Further, as noted above, Set B is the two dimensional library that consists of all permutations of all of the variants of R^1 represented in Set A and a set of R^2 variants listed above with R^3 fixed as 2-(trifluoromethyl)pyridin-5-ylmethyl. Were one to vary R^1 and R^2 and R^3, a three dimensional library of example compounds would result. Set C is the three dimensional library that consists of all permutations of all of the variants of R^1 represented in Set A, all of the R^2 variants listed above for Set B, and a set of R^3 variants listed below. In Set C, R^4 is methyl, R^5 is O, n is single bond and m is double bond. The compounds of Set C may be prepared by one skilled in the art by the methods described above. The compounds of Set C are meant to further illustrate the scope of the invention without being limiting in any way.

R^3 variants of Set C:

- 50 -
Further, as noted above, Set C is the three dimensional library that consists of all permutations of all of the variants of R¹ represented in Set A, all variants of R² represented in Set B, and variants listed above with R⁴ fixed as methyl, R⁵ is O, n is single bond and m is double bond. Were one to vary R¹ and R² and R³, a three dimensional library of example compounds would result. Set D is the four dimensional library that consists of all permutations of all of the variants of R¹ represented in Set A, all of the R² variants listed above for Set B, all of the R³ variants listed above for Set C and a set of R⁴, R⁵, n and m variants listed below. The compounds of Set D may be prepared by one skilled in the art by the methods described above. The compounds of Set D are meant to further illustrate the scope of the invention without being limiting in any way.

R⁴, R⁵ n and m variants of Set D are depicted as a fragment of the depiction represents a compound of formula I wherein R⁴ is methyl, R⁵ is O, n is single bond and m is double bond).
$R^4, R^5 n$ and $m$ variants of Set D:
Biological Evaluation

Cannabinoid Receptor Binding Assay

Radioligand binding studies were conducted in membranes prepared from Chinese Hamster Ovary (CHO) cells that over-express recombinant human CB-1 (CHO-CB-1 cells). Total assay volume for the binding studies was 100 µl. 5 µg of membranes were brought up to a final volume of 95 µl with Binding Buffer (25 mM HEPES, 150 mM NaCl, 2.5 mM CaCl₂, 1 mM MgCl₂, 0.25% BSA). The diluted membranes were preincubated with a compound or DMSO vehicle. The binding reaction was initiated by the addition of 2 nM final ³H-CP-55,940 (120 Ci/mmol) and proceeded for 2.5 hours at room temperature. The binding reaction was terminated by transferring the reaction to GF/B 96 well plates (presoaked with 0.3% polyethylenimine) using a Packard Cell Harvester. The filter was washed with 0.25x PBS, 30 µl MicroScint was added per well, and the bound radiolabel was quantitated by scintillation counting on a Packard TopCount Scintillation Counter. The CB-2 radioligand binding assay was conducted identically except that the membranes from CHO-CB-2 cells were used.

For a compound to be considered a CB-1 antagonist, the compound must possess a CB-1 receptor binding affinity Ki less than 13000 nM. As determined by the assay described above, the CB-1 receptor binding Ki values of working Examples 1-63 fall within the range of 0.01 nM to 10000 nM.

Cannabinoid Receptor Functional Activity Assay

Functional CB-1 inverse agonist activity of test compounds was determined in CHO-CB-1 cells using a cAMP accumulation assay. CHO-CB-1 cells were grown in 96 well plates to near confluence. On the day of the functional assay, growth medium was aspirated and 100 of Assay Buffer (PBS plus 25 mM HEPES / 0.1 mM 3-isobutyl-1-methylxanthine/ 0.1% BSA) was added. Compounds were added to the Assay buffer diluted 1:100 from 100% DMSO and allowed to preincubate for 10 minutes prior to addition of 5 µM forskolin. The mixture was allowed to proceed for 15 minutes at room temperature and was terminated by the addition of 0.1 N HCl. The total intracellular cAMP concentration was quantitated using the Amersham cAMP SPA kit.
UTILITIES AND COMBINATIONS

Utilities

The compounds of the present invention are cannabinoid receptor modulators, and include compounds which are, for example, selective agonists, partial agonists, inverse agonists, antagonists or partial antagonists of the cannabinoid receptor. Accordingly, the compounds of the present invention may be useful for the treatment or prevention of diseases and disorders associated with G-protein coupled cannabinoid receptor activity. Preferably, compounds of the present invention possess activity as antagonists or inverse agonists of the CB-1 receptor, and may be used in the treatment of diseases or disorders associated with the activity of the CB-1 receptor.

Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to metabolic and eating disorders as well as conditions associated with metabolic disorders, (e.g., obesity, diabetes, arteriosclerosis, hypertension, polycystic ovary disease, cardiovascular disease, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, cholelithiasis and sleep disorders, hyperlipidemic conditions, bulimia nervosa and compulsive eating disorders) or psychiatric disorders, such as substance abuse, depression, anxiety, mania and schizophrenia. These compounds could also be used for the improvement of cognitive function (e.g., the treatment of dementia, including Alzheimer’s disease, short term memory loss and attention deficit disorders); neurodegenerative disorders (e.g., Parkinson’s Disease, cerebral apoplexy and craniocerebral trauma) and hypotension (e.g., hemorrhagic and endotoxin-induced hypotension). These compounds could also be used for treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency; treatment of cardiac dysfunction (e.g., associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure); and improvement of the overall pulmonary function; transplant rejection; rheumatoid arthritis; multiple sclerosis; inflammatory bowel disease; lupus; graft vs. host disease; T-cell mediated hypersensitivity disease; psoriasis; asthma; Hashimoto's thyroiditis;
Guillain-Barre syndrome; cancer; contact dermatitis; allergic rhinitis; and ischemic or reperfusion injury.

Compounds useful in the treatment of appetitive or motivational disorders regulate desires to consume sugars, carbohydrates, alcohol or drugs and more generally to regulate the consumption of ingredients with hedonic value. In the present description and in the claims, appetitive disorders are understood as meaning: disorders associated with a substance and especially abuse of a substance and/or dependency on a substance, disorders of eating behaviors, especially those liable to cause excess weight, irrespective of its origin, for example: bulimia nervosa, craving for sugars. The present invention therefore further relates to the use of a CB-1 receptor antagonist or inverse agonist for the treatment of bulimia and obesity, including obesity associated with type II diabetes (non-insulin-dependent diabetes), or more generally any disease resulting in the patient becoming overweight. Obesity, as described herein, is defined by a body mass index (kg/m²) of at least 26. It may be due to any cause, whether genetic or environmental, including overeating and bulimia, polycystic ovary disease, craniopharyngeoma, Prader-Willi Syndrome, Frohlich’s Syndrome, Type II diabetes, growth hormone deficiency, Turner’s Syndrome and other pathological states characterized by reduced metabolic activity or reduced energy expenditure. As used with reference to the utilities described herein, the term "treating" or "treatment" encompasses prevention, partial alleviation, or cure of the disease or disorder. Further, treatment of obesity is expected to prevent progression of medical covariants of obesity, such as arteriosclerosis, Type II diabetes, polycystic ovary disease, cardiovascular disease, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, cholelithiasis and sleep disorders.

Compounds in the present invention may also be useful in treating substance abuse disorders, including substance dependence or abuse without physiological dependence. Substances of abuse include alcohol, amphetamines (or amphetamine-like substances), caffeine, cannabis, cocaine, hallucinogens, inhalents, nicotine, opioids, phencyclidine (or phencyclidine-like compounds), sedative-hypnotics or benzodiazepines, and other (or unknown) substances and combinations of the above. The terms "substance abuse disorders" also includes drug or alcohol withdrawal.
syndromes and substance-induced anxiety or mood disorder with onset during withdrawal.

Compounds in the present invention may be useful in treating memory impairment and cognitive disorders. The condition of memory impairment is manifested by impairment of the ability to learn new information and/or the inability to recall previously learned information. Memory impairment is a primary symptom of dementia and can also be a symptom associated with such diseases as Alzheimer's disease, schizophrenia, Parkinson's disease, Huntington's disease, Pick's disease, Creutzfeld-Jakob disease, HIV, cardiovascular disease, and head trauma as well as age-related cognitive decline. Dementias are diseases that include memory loss and additional intellectual impairment separate from memory. Cannabinoid receptor modulators may also be useful in treating cognitive impairments related to attentional deficits, such as attention deficit disorder.

Compounds in the present invention may also be useful in treating diseases associated with dysfunction of brain dopaminergic systems, such as Parkinson's Disease and substance abuse disorders. Parkinson's Disease is a neurodegenerative movement disorder characterized by bradykinesia and tremor.

As modulators of the cannabinoid receptor, the compounds of the present invention are further useful for the treatment and prevention of respiratory diseases and disorders. Respiratory diseases for which cannabinoid receptor modulators are useful include, but are not limited to, chronic pulmonary obstructive disorder, emphysema, asthma, and bronchitis. In addition, cannabinoid receptor modulators block the activation of lung epithelial cells by moieties such as allergic agents, inflammatory cytokines or smoke, thereby limiting release of mucin, cytokines, and chemokines, or selectively inhibiting lung epithelial cell activation.

Moreover, the compounds employed in the present invention may stimulate inhibitory pathways in cells, particularly in leukocytes, lung epithelial cells, or both, and are thus useful in treating such diseases. "Leukocyte activation" is defined herein as any or all of cell proliferation, cytokine production, adhesion protein expression, and production of inflammatory mediators. "Epithelial cell activation" is defined herein as the production of any or all of mucins, cytokines, chemokines, and adhesion protein expression.
Use of the compounds of the present invention for treating leukocyte activation-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: transplant (such as organ transplant, acute transplant, xenotransplant or heterograft or hernoograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); multiple sclerosis; respiratory and pulmonary diseases including but not limited to chronic obstructive pulmonary disease (COPD), emphysema, bronchitis, and acute respiratory distress syndrome (ARDS); inflammatory bowel disease, including ulcerative colitis and Crohn's disease; lupus (systemic lupus erythematosus); graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy (Celiac disease); psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease; Addison's disease (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituitarism; Guillain-Barre syndrome; other autoimmune diseases; glomerulonephritis; serum sickness; urticaria; allergic diseases such as respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleroderma; mycosis fungoides; acute inflammatory and respiratory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplantaris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic sclerosis; and morphea. The term "leukocyte activation-associated" or "leukocyte-activation mediated" disease as used herein includes each of the above referenced diseases or disorders. In a particular embodiment, the compounds of the present invention are useful for treating the aforementioned exemplary disorders irrespective of their etiology. The combined activity of the present compounds towards monocytes, macrophages, T-cells, etc. may be useful in treating any of the above-mentioned disorders.
Cannabinoid receptors are important in the regulation of Fc gamma receptor responses of monocytes and macrophages. Compounds of the present invention inhibit the Fc gamma dependent production of TNF alpha in human monocytes/macrophages. The ability to inhibit Fc gamma receptor dependent monocyte and macrophage responses results in additional anti-inflammatory activity for the present compounds. This activity is especially of value, for example, in treating inflammatory diseases such as arthritis or inflammatory bowel disease. In particular, the present compounds are useful for treating autoimmune glomerulonephritis and other instances of glomerulonephritis induced by deposition of immune complexes in the kidney that trigger Fc gamma receptor responses leading to kidney damage.

Cannabinoid receptors are expressed on lung epithelial cells. These cells are responsible for the secretion of mucins and inflammatory cytokines/chemokines in the lung and are thus intricately involved in the generation and progression of respiratory diseases. Cannabinoid receptor modulators regulate both the spontaneous and the stimulated production of both mucins and cytokines. Thus, such compounds are useful in treating respiratory and pulmonary diseases including, COPD, ARDS, and bronchitis.

Further, cannabinoid receptors may be expressed on gut epithelial cells and hence regulate cytokine and mucin production and may be of clinical use in treating inflammatory diseases related to the gut. Cannabinoid receptors are also expressed on lymphocytes, a subset of leukocytes. Thus, cannabinoid receptor modulators will inhibit B and T-cell activation, proliferation and differentiation. Thus, such compounds will be useful in treating autoimmune diseases that involve either antibody or cell mediated responses such as multiple sclerosis and lupus.

In addition, cannabinoid receptors regulate the Fc epsilon receptor and chemokine induced degranulation of mast cells and basophils. These play important roles in asthma, allergic rhinitis, and other allergic disease. Fc epsilon receptors are stimulated by IgE-antigen complexes. Compounds of the present invention inhibit the Fc epsilon induced degranulation responses, including the basophil cell line, RBL.

The ability to inhibit Fc epsilon receptor dependent mast cell and basophil responses results in additional anti-inflammatory and anti-allergic activity for the present
compounds. In particular, the present compounds are useful for treating asthma, allergic rhinitis, and other instances of allergic disease.

**Combinations**

The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention can be used alone, in combination with other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-obesity agents; anti-diabetic agents, appetite suppressants; cholesterol/lipid-lowering agents, HDL-raising agents, cognition enhancing agents, agents used to treat neurodegeneration, agents used to treat respiratory conditions, agents used to treat bowel disorders, anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; cardiac glycosides; and anti-tumor agents.

Such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the cannabinoid receptor modulators in accordance with the invention.

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include melanocortin receptor (MC4R) agonists, melanin-concentrating hormone receptor (MCHR) antagonists, growth hormone secretagogue receptor (GHSR) antagonists, galanin receptor modulators, orexin antagonists, CCK agonists, GLP-1 agonists, and other Pre-proglucagon-derived peptides; NPY1 or NPY5 antagonists, NPY2 and NPY4 modulators, corticotropin releasing factor agonists, histamine receptor-3 (H3) modulators, aP2 inhibitors, PPAR gamma modulators, PPAR delta modulators, acetyl-CoA carboxylase (ACC) inhibitors, 11-β-HSD-1 inhibitors, adiponectin receptor modulators; beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a thyroid receptor beta modulator, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), a lipase inhibitor, such as orlistat
or ATL-962 (Alizyme), serotonin receptor agonists, (e.g., BVT-933 (Biovitrum)), monoamine reuptake inhibitors or releasing agents, such as fenfluramine, dexfenfluramine, fluvoxamine, fluoxetine, paroxetine, sertraline, chlorphentermine, cloforex, clortermine, picilorex, sibutramine, dexamphetamine, phentermine, phenylpropanolamine or mazindol, anorectic agents such as topiramate (Johnson & Johnson), CNTF (ciliary neurotrophic factor) /Axokine® (Regeneron), BDNF (brain-derived neurotrophic factor), leptin and leptin receptor modulators, or cannabinoid-1 receptor antagonists, such as SR-141716 (Sanofi) or SLV-319 (Solvay).

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include: insulin secretagogues or insulin sensitizers, which may include biguanides, sulfonyl ureas, glucosidase inhibitors, aldose reductase inhibitors, PPAR γ agonists such as thiazolidinediones, PPAR α agonists (such as fibric acid derivatives), PPAR δ antagonists or agonists, PPAR α/γ dual agonists, 11-β-HSD-1 inhibitors, dipeptidyl peptidase IV (DP4) inhibitors, SGLT2 inhibitors, glycogen phosphorylase inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1), GLP-1 agonist, and/or a PTP-1B inhibitor (protein tyrosine phosphatase-1B inhibitor).

The antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl. Where the antidiabetic agent is a biguanide, the compounds of the present invention will be employed in a weight ratio to biguanide within the range from about 0.001:1 to about 10:1, preferably from about 0.01:1 to about 5:1.

The antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the beta-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms. The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S. Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.
The compounds of the present invention may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi’s MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Wellcome’s GL-262570, enligltxone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

The compounds of the present invention may be employed with a PPARα/γ dual agonist such as MK-767/KRP-297 (Merck/Kyorin; as described in, K. Yajima, et. al., *Am. J. Physiol. Endocrinol. Metab.*, 284: E966-E971 (2003)), AZ-242 (tesaglitazar; Astra-Zeneca; as described in B. Ljung, et. al., *J. Lipid Res.*, 43, 1855-1863 (2002)); muraglitazar; or the compounds described in US patent 6,414,002.

The compounds of the present invention may be employed in combination with anti-hyperlipidemia agents, or agents used to treat arteriosclerosis. An example of an hypolipidemic agent would be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, pitavastatin (Nissan/Sankyo’s nisvastatin (NK-104) or itavastatin), disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca rosuvastatin (visastatin (ZD-4522)) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle’s SC-45355 (a 3-substituted
pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No. 0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent Nos. 5,506,219 and 5,691,322. In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.


Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (SECHOLEX, POLICLEXIDE) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-
Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrodipristatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyaku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid (niacin), acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallyl methylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.


The hypolipidemic agent may be an upregulator of LDL receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).
hylipidemic agent may be a cholesterol absorption inhibitor preferably Schering-
Plough’s SCH48461 (ezetimibe) as well as those disclosed in \textit{Atherosclerosis} 115, 45-

The other lipid agent or lipid-modulating agent may be a cholesteryl transfer
protein inhibitor (CETP) such as Pfizer’s CP-529,414 as well as those disclosed in
WO/0038722 and in EP 818448 (Bayer) and EP 992496, and Pharmacia’s SC-744 and
SC-795, as well as CETI-1 and JTT-705.

The hypolipidemic agent may be an ileal Na⁺/bile acid cotransporter inhibitor
such as disclosed in Drugs of the Future, 24, 425-430 (1999). The ATP citrate lyase
inhibitor which may be employed in the combination of the invention may include, for
example, those disclosed in U.S. Patent No. 5,447,954.

The other lipid agent also includes a phytoestrogen compound such as
disclosed in WO 00/30665 including isolated soy bean protein, soy protein
concentrate or soy flour as well as an isoflavone such as genistein, daidzein, glycine
or equol, or phytoesters, phytostanol or tocotrienol as disclosed in WO 2000/015201;
a beta-lactam cholesterol absorption inhibitor such as disclosed in EP 675714; an
HDL upregulator such as an LXR agonist, a PPAR α-agonist and/or an FXR agonist;
an LDL catabolism promoter such as disclosed in EP 102272; a sodium-proton
exchange inhibitor such as disclosed in DE 19622222; an LDL-receptor increaser or a
steroidal glycoside such as disclosed in U.S. Patent No. 5,698,527 and GB 2304106;
an anti-oxidant such as beta-carotene, ascorbic acid, α-tocopherol or retinol as
disclosed in WO 94/15592 as well as Vitamin C and an antimycocystine agent such
as folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E; isoniazid as disclosed
in WO 97/35576; a cholesterol absorption inhibitor, an HMG-CoA synthesize inhibitor,
or a lanosterol demethylase inhibitor as disclosed in WO 97/48701; a PPAR δ agonist
for treating dyslipidemia; or a sterol regulating element binding protein-I (SREBP-1)
as disclosed in WO 2000/050574, for example, a sphingolipid, such as ceramide, or
neutral sphingomyelenase (N-SMase) or fragment thereof. Preferred hypolipidemic
agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, pitavastatin
and rosuvastatin, as well as niacin and/or cholestagel.
The compounds of the present invention may be employed in combination with anti-hypertensive agents. Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and/or T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine,bumetanide, triamterene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

Cannabinoid receptor modulators could be useful in treating other diseases associated with obesity, including sleep disorders. Therefore, the compounds described in the present invention could be used in combination with therapeutics for treating sleep disorders. Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present invention include melatonin analogs, melatonin receptor antagonists, ML 1 B agonists, GABA receptor modulators; NMDA receptor modulators, histamine-3 (H3) receptor modulators, dopamine agonists and orexin receptor modulators.

Cannabinoid receptor modulators may reduce or ameliorate substance abuse or addictive disorders. Therefore, combination of cannabinoid receptor modulators with agents used to treat addictive disorders may reduce the dose requirement or improve the efficacy of current addictive disorder therapeutics. Examples of agents used to treat substance abuse or addictive disorders are: selective serotonin reuptake inhibitors (SSRI), methadone, buprenorphine, nicotine and bupropion.

Cannabinoid receptor modulators may reduce anxiety or depression; therefore, the compounds described in this application may be used in combination with anti-
anxiety agents or antidepressants. Examples of suitable anti-anxiety agents for use in combination with the compounds of the present invention include benzodiazepines (e.g., diazepam, lorazepam, oxazepam, alprazolam, chlordiazepoxide, clonazepam, chlorazepate, halazepam and prazepam), 5HT1A receptor agonists (e.g., buspirone, flesinoxan, gepirone and ipsapirone), and corticotropin releasing factor (CRF) antagonists.

Examples of suitable classes of anti-depressants for use in combination with the compounds of the present invention include norepinephrine reuptake inhibitors (tertiary and secondary amine tricyclics), selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, fluvoxamine, paroxetine and sertraline), monoamine oxidase inhibitors (MAOIs) (isocarboxazid, phenelzine, tranylcypromine, selegiline), reversible inhibitors of monoamine oxidase (RIMAs) ( moclobemide), serotonin and norepinephrine reuptake inhibitors (SNRIs) (venlafaxine), corticotropin releasing factor (CRF) receptor antagonists, alpah-adrenoreceptor antagonists, and atypical antidepressants (bupropion, lithium, nefazodone, trazodone and viloxazine).

The combination of a conventional antipsychotic drug with a CB-1 receptor antagonist could also enhance symptom reduction in the treatment of psychosis or mania. Further, such a combination could enable rapid symptom reduction, reducing the need for chronic treatment with antipsychotic agents. Such a combination could also reduce the effective antipsychotic dose requirement, resulting in reduced probability of developing the motor dysfunction typical of chronic antipsychotic treatment.

Examples of suitable antipsychotic agents for use in combination with the compounds of the present invention include the phenothiazine (chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine), thioxanthine (chlorprothixene, thiothixene), heterocyclic dibenzazepine (clozapine, olanzepine and aripiprazole), butyrophenone (haloperidol), dipheyylbutylpiperidine (pimozide) and indolone (molindone) classes of antipsychotic agents. Other antipsychotic agents with potential therapeutic value in combination with the compounds in the present invention include loxapine, sulpiride and risperidone.
Combination of the compounds in the present invention with conventional antipsychotic drugs could also provide an enhanced therapeutic effect for the treatment of schizophrenic disorders, as described above for manic disorders. As used here, schizophrenic disorders include paranoid, disorganized, catatonic, undifferentiated and residual schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder and psychotic disorder not specified. Examples of suitable antipsychotic drugs for combination with the compounds in the present invention include the antipsychotics mentioned above, as well as dopamine receptor antagonists, muscarinic receptor agonists, 5HT2A receptor antagonists and 5HT2A/dopamine receptor antagonists or partial agonists (e.g., olanzepine, aripiprazole, risperidone, ziprasidone).

The compounds described in the present invention could be used to enhance the effects of cognition-enhancing agents, such as acetylcholinesterase inhibitors (e.g., tacrine), muscarinic receptor-1 agonists (e.g., milameline), nicotinic agonists, glutamic acid receptor (AMPA and NMDA) modulators, and nootropic agents (e.g., piracetam, levetiracetam). Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present invention include donepezil, tacrine, revastigaine, 5HT6, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs blockers.

The compounds described in the present invention could be used to enhance the effects of agents used in the treatment of Parkinson’s Disease. Examples of agents used to treat Parkinson’s Disease include: levadopa with or without a COMT inhibitor, antiglutamatergic drugs (amantadine, riluzole), alpha-2 adrenergic antagonists such as idazoxan, opiate antagonists, such as naltrexone, other dopamine agonists or transporter modulators, such as ropinirole, or pramipexole or neurotrophic factors such as glial derived neurotrophic factor (GDNF).

The compounds described in the present invention could be used in combination with suitable anti-inflammatory agents. Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen,
piroxicam, Naproxen®, Celebrex®, Vioxx®, CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®), integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384, including TNF-alpha inhibitors, such as tenidap, anti-TNF antibodies or soluble TNF receptor such as etanercept (Enbrel®), rapamycin (sirolimus or Rapamune) and leflunomide (Arava)), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome (e.g., Zelnorm® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

Exemplary of such other therapeutic agents which may be used in combination with cannabinoid receptor modulators include the following: cyclosporins (e.g., cyclosporin A), anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, monoclonal antibody OKT3, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40Ig and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine and cyclophosphamide, anticytokines such as antII-L-4 or IL-4 receptor fusion proteins and PDE 4 inhibitors such as Ariflo, and the PTK inhibitors disclosed in the following U.S. patent applications, incorporated herein by reference in their entirety: Ser. No. 09/097,338, filed Jun. 15, 1998; Ser. No. 09/094,797, filed Jun. 15, 1998; Ser. No. 09/173,413, filed Oct. 15, 1998; and Ser. No. 09/262,525, filed Mar. 4, 1999. See also the following documents and references cited therein and incorporated herein by reference: Hollenbaugh, D., et al., "Cleavable CD40Ig Fusion Proteins and the Binding to Sgp39", J. Immunol. Methods (Netherlands), 188 (1), pp. 1-7 (Dec. 15, 1995); Hollenbaugh, D., et al., "The Human T Cell Antigen Gp39, A Member of the TNF Gene Family, Is a Ligand for the CD40 Receptor: Expression of a Soluble Form of Gp39 with B Cell Co-Stimulatory
Activity", *EMBO J* (England), 11 (12), pp. 4313-4321 (December 1992); and
Moreland, L. W. et al., "Treatment of Rheumatoid Arthritis with a Recombinant
Human Tumor Necrosis Factor Receptor (P75)-Fc Fusion Protein," *New England J. of

The above other therapeutic agents, when employed in combination with the
compounds of the present invention, may be used, for example, in those amounts
indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one
of ordinary skill in the art.

The compounds of formula (I) of the invention can be administered orally or
parenterally, such as subcutaneously or intravenously, as well as by nasal application,
rectally or sublingually to various mammalian species known to be subject to such
maladies, e.g., humans, in an effective amount up to 1 gram, preferably up to 200 mg,
more preferably to 50 mg in a regimen of single, two or four divided daily doses.

The compounds of the formula (I) can be administered for any of the uses
described herein by any suitable means, for example, orally, such as in the form of
tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by
subcutaneous, intravenous, intramuscular, or intravascular injection or infusion
techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or
suspensions); nasally, including administration to the nasal membranes, such as by
inhalation spray; topically, such as in the form of a cream or ointment; or rectally such
as in the form of suppositories; in dosage unit formulations containing non-toxic,
pharmaceutically acceptable vehicles or diluents. The present compounds can, for
example, be administered in a form suitable for immediate release or extended release.
Immediate release or extended release can be achieved by the use of suitable
pharmaceutical compositions comprising the present compounds, or, particularly in
the case of extended release, by the use of devices such as subcutaneous implants or
osmotic pumps. The present compounds can also be administered liposomally.

Exemplary compositions for oral administration include suspensions which
can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or
sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and
sweeteners or flavoring agents such as those known in the art; and immediate release
tablets which can contain, for example, microcrystalline cellulose, dicalcium
phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula (I) can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer’s solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Exemplary compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors.
including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

5 It should be understood that while this invention has been described herein in terms of specific embodiments set forth in detail, such embodiments are presented by way of illustration of the general principles of the invention, and the invention is not necessarily limited thereto. Certain modifications and variations in any given material, process step or chemical formula will be readily apparent to those skilled in the art without departing from the true spirit and scope of the present invention, and all such modifications and variations should be considered within the scope of the claims that follow.
WHAT IS CLAIMED IS:

1. The compound of formula I,

   \[
   \begin{array}{c}
   \text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4, \text{R}^5 \\
   \end{array}
   \]

   including all pharmaceutically acceptable salts and stereoisomers,

   wherein:

   R\(^1\) is selected from the group consisting of halogen, cyano, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -NR\(^8\)R\(^9\), -CO\(_2\)R\(^8\), -CONR\(^8\)R\(^9\), -OR\(^8\), -NR\(^8\)COR\(^9\), -NR\(^8\)CONR\(^8\)R\(^9\), -NR\(^8\)CO\(_2\)R\(^9\), -OCONR\(^8\)R\(^9\), -NR\(^8\)S(O)\(_p\)R\(^9\), -NR\(^8\)S(O)\(_p\)NR\(^8\)R\(^9\), -NR\(^8\)S(O)\(_p\)OR\(^9\) and -OS(O)\(_p\)NR\(^8\)R\(^9\);

   R\(^2\) is selected from the group consisting of halogen, cyano, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -NR\(^8\)R\(^9\), -CO\(_2\)R\(^8\), -CONR\(^8\)R\(^9\), -OR\(^8\), -NR\(^8\)COR\(^9\), -NR\(^8\)CONR\(^8\)R\(^9\), -NR\(^8\)CO\(_2\)R\(^9\), -OCONR\(^8\)R\(^9\), -NR\(^8\)S(O)\(_p\)R\(^9\), -NR\(^8\)S(O)\(_p\)NR\(^8\)R\(^9\), -NR\(^8\)S(O)\(_p\)OR\(^9\) and -OS(O)\(_p\)NR\(^8\)R\(^9\);

   R\(^3\) is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

   R\(^4\) is absent when n is a double bond;

   R\(^4\) is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl when n is a single bond;

   R\(^5\) is selected from the group consisting of halogen, -OR\(^8\), -NR\(^8\)R\(^9\), -OCONR\(^8\)R\(^9\), -NCR\(^8\), -NCO\(_2\)R\(^8\) and -NR\(^8\)S(O)\(_p\)R\(^9\) when m is a single bond,
wherein the $R^5$ group has a molecular weight of less than 200 atomic mass units;

$R^5$ is O when m is a double bond;

$R^8$ and $R^9$ are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocycl, heterocycloalkyl, aryl, heteroaryl and heteroarylalkyl;

$R^8$ and $R^9$ can together form a 4, 5, 6, or 7 membered heterocyclyl ring or a 5 or 6 membered heteroaryl ring;

m is a single or double bond;

n is a single or double bond;

when m is a single bond, n is a double bond;

when m is a double bond, n is a single bond; and

p is an integer of 1 or 2.

2. The compound according to Claim 1, wherein:

$R^1$ is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclylalkyl, aryl, aryalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -OR$^8$ and -NR$^8$R$^9$;

$R^2$ is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycl, heterocyclylalkyl, aryl, aryalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -OR$^8$ and -NR$^8$R$^9$;

$R^3$ is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aryalkyl, heteroaryl and heteroarylalkyl;

$R^4$ is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aryalkyl, heteroaryl and heteroarylalkyl;

$R^5$ is O;

$R^8$ and $R^9$ are independently selected from H, alkyl, aryalkyl, cycloalkyl, heterocycl, heterocycloalkyl, aryl, heteroaryl and heteroarylalkyl;

$R^8$ and $R^9$ can together form a 4, 5, 6, or 7 membered heterocyclyl ring or a 5 or 6 membered heteroaryl ring;

m is a double bond; and
n is a single bond.

3. The compound according to Claim 2, wherein:
   R¹ is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;
   R² is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;
   R³ is selected from the group consisting of H, alkyl, cycloalkyl and heterocyclyl;
   R⁴ is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;
   R⁵ is O;
   R⁸ and R⁹ are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, aryl, heteroaryl and heteroarylalkyl;
   R⁸ and R⁹ can together form a 4, 5, 6, or 7 membered heterocyclyl ring or a 5 or 6 membered heteroaryl ring;
   m is a double bond; and
   n is a single bond.

4. The compound according to Claim 3, wherein:
   R² is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹.

5. The compound according to Claim 4, wherein:
   R¹ is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹.

6. The compound according to Claim 5, wherein:
R⁴ is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycyl, heterocycylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl.

7. The compound according to Claim 1, wherein:
R¹ is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;
R² is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;
R³ is selected from the group consisting of H, alkyl, cycloalkyl and heterocycyl;
R⁴ is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocycyl, heterocycylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;
R⁵ is O;
R⁸ and R⁹ are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocycyl, heterocycylalkyl, aryl, heteroaryl and heteroarylalkyl;
R⁸ and R⁹ can together form a 4, 5, 6, or 7 membered heterocyclyl ring or a 5 or 6 membered heteroaryl ring;
m is a double bond; and
n is a single bond.

8. The compound according to Claim 1, wherein:
R¹ is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycyl, heterocycylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;
R² is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocycyl, heterocycylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;
R³ is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocycyl, heterocycylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;
R\(^4\) is selected from the group consisting of H, alkyl, cycloalkyl and heterocyclol;

R\(^5\) is O;

R\(^8\) and R\(^9\) are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclol, heterocycloalkyl, aryl, heteroaryl and heteroaryalkyl;

R\(^8\) and R\(^9\) can together form a 4, 5, 6, or 7 membered heterocyclol ring or a 5 or 6 membered heteroaryl ring;

m is a double bond; and

n is a single bond.

9. The compound according to Claim 8, wherein:

R\(^2\) is selected from the group consisting of heterocyclol, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, arloxy, heteroaryloxy, -OR\(^8\) and -NR\(^8\)R\(^9\).

10. The compound according to Claim 9, wherein:

R\(^1\) is selected from the group consisting of heterocyclol, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, arloxy, heteroaryloxy, -OR\(^8\) and -NR\(^8\)R\(^9\).

11. The compound according to Claim 10, wherein:

R\(^3\) is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclol, heterocycloalkyl, aryl, arylalkyl, heteroaryl and heteroaryalkyl.

12. The compound according to Claim 1, wherein:

R\(^1\) is selected from the group consisting of aryl, heteroaryl, arloxy, heteroaryloxy, -OR\(^8\) and -NR\(^8\)R\(^9\);

R\(^2\) is selected from the group consisting of aryl, heteroaryl, arloxy, heteroaryloxy, -OR\(^8\) and -NR\(^8\)R\(^9\);

R\(^3\) is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclol, heterocycloalkyl, aryl, arylalkyl, heteroaryl and heteroaryalkyl;

R\(^4\) is selected from the group consisting of H and alkyl;
R² is O;

R⁴ and R⁵ are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heterocycloalkyl, aryl, heteroaryl and heteroaryalkyl;

R⁴ and R⁵ can together form a 4, 5, 6, or 7 membered heterocyclyl ring or a 5 or 6 membered heteroaryl ring;

m is a double bond; and

n is a single bond.

13. The compound according to Claim 1, wherein:

R¹ is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;

R² is selected from the group consisting of alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroaryalkyl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;

R³ is selected from the group consisting of H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl and heteroaryalkyl;

R⁴ is absent;

R⁵ is selected from the group consisting of halogen, -OR⁸, -NR⁸R⁹, -OCONR⁸R⁹, -NCR⁸, -NCO₂R⁸, -NR⁸S(O)₂R⁹ when m is a single bond, wherein the R⁵ group has a molecular weight of less than 200 atomic mass units;

R⁸ and R⁹ are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heterocycloalkyl, aryl, heteroaryl and heteroaryalkyl;

R⁸ and R⁹ can together form a 4, 5, 6, or 7 membered heterocyclyl ring or a 5 or 6 membered heteroaryl ring;

m is a single bond; and

n is a double bond.

14. The compound according to Claim 13, wherein:
R² is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaaryloxy, -OR⁸ and -NR⁸R⁹.

15. The compound according to Claim 14, wherein:

R¹ is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaaryloxy, -OR⁸ and -NR⁸R⁹.

16. The compound according to Claim 15, wherein:

R³ is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl.

17. The compound according to Claim 16, wherein:

R⁵ is selected from the group consisting of -OR⁸ and -NR⁸R⁹;

wherein the R⁵ group has a molecular weight of less than 200 atomic mass units;

18. The compound according to Claim 1, wherein:

R¹ is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;

R² is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, -OR⁸ and -NR⁸R⁹;

R³ is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl;

R⁵ is selected from the group consisting of -OR⁸, -NR⁸R⁹;

wherein the R⁵ group has a molecular weight of less than 200 atomic mass units;

R⁸ and R⁹ are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, heterocycloalkyl, aryl, heteroaryl and heteroarylalkyl;

R⁸ and R⁹ can together form a 4, 5, 6, or 7 membered heterocyclyl ring or a 5 or 6 membered heteroaryl ring;
m is a single bond; and
n is a double bond.

19. The compound of Claim 1 selected from:
20. The compound of Claim 1 selected from:
21. The compound of Claim 1 selected from:

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22. A pharmaceutical composition, comprising:
at least one compound according to Claim 1; and
at least one pharmaceutically acceptable diluent or carrier.

23. A pharmaceutical composition, comprising:
at least one compound according to Claim 1;
at least one other therapeutic agent; and
at least one pharmaceutically acceptable diluent or carrier.
24. A method for treating a cannabinoid receptor mediated disease or disorder, comprising: administering to a patient in need of treatment a therapeutically effective amount of a compound according to Claim 1.

25. A pharmaceutical combination comprising a pharmaceutical composition of Claim 22 and a therapeutic agent selected from anti-obesity agents; appetite suppressants; anti-diabetic agents; anti-hyperlipidemia agents; hypolipidemic agents; hypocholesterolemic agents; lipid-modulating agents; cholesterol-lowering agents; lipid-lowering agents; HDL-raising agent, anti-hypertensive agents; agents used to treat sleep disorders; agents used to treat substance abuse and addictive disorders; anti-anxiety agents; anti-depressants; anti-psychotic agents; cognition enhancing agents; agents used to treat cognitive disorders; agents used to treat Alzheimer’s disease; agents used to treat Parkinson’s disease; anti-inflammatory agents; agents used to treat neurodegeneration; agents used to treat arteriosclerosis; agents used to treat respiratory conditions; agents used to treat bowel disorders; cardiac glycosides; and anti-tumor agents.

26. A pharmaceutical combination of Claim 25 wherein the other therapeutic agent may be administered prior to, simultaneously with, or following the administration of the pharmaceutical composition of Claim 22.

27. A pharmaceutical combination of Claim 25 wherein the anti-obesity agent is selected from melanocortin receptor (MC4R) agonists; melanin-concentrating hormone receptor (MCHR) antagonists; growth hormone secretagogue receptor (GHSR) antagonists; galanin receptor modulators; orexin antagonists; CCK agonists; GLP-1 agonists and other pPre-proglucagon-derived peptides; NPY1 or NPY5 antagonists; NPY2 and NPY4 modulators; corticotropin releasing factor agonists; histamine receptor-3 (H3) modulators; aP2 inhibitors; PPAR gamma modulators; PPAR delta modulators; acetyl-CoA carboxylase (ACC) inhibitors; 11-β-HSD-1 inhibitors; adiponectin receptor modulators; beta 3 adrenergic agonists, including AJ9677, L750355 and CP331648 or other known beta 3 agonists; thyroid receptor beta modulator; lipase inhibitors, including orlistat and ATL-962; serotonin receptor
agonists, including BVT-933; monoamine reuptake inhibitors or releasing agents, including fenfluramine, dexfenfluramine, fluvoxamine, fluoxetine, paroxetine, sertraline, chlorphentermine, cloforex, clortermine, picilorex, sibutramine, dexamphetamine, phentermine, phenylpropanolamine and mazindol; anorectic agents, including topiramate; ciliary neurotrophic factor, including Axokine; brain-derived neurotrophic factor; leptin and leptin receptor modulators and other cannabinoid-1 receptor antagonists, including SR-141716 and SLV-319.

28. A pharmaceutical combination of Claim 25 wherein the anti-diabetic agent is selected from insulin secretagogues; insulin sensitizers; anti-hyperglycemic agents; biguanides; sulfonyl ureas; glucosidase inhibitors; aldose reductase inhibitors; PPAR γ agonists including thiazolidinediones; PPAR α agonists, including fibric acid derivatives; PPAR δ antagonists or agonists; PPAR α/γ dual agonists; 11-β-HSD-1 inhibitors; dipeptidyl peptidase IV inhibitors; SGLT2 inhibitors; glycogen phosphorylase inhibitors; meglitinides; insulin; glucagon-like peptide-1; glucagon-like peptide 1 agonists; and protein tyrosine phosphatase-1B inhibitors.

29. A pharmaceutical combination of Claim 28 wherein the anti-diabetic agent is an oral antihyperglycemic agent selected from the biguanides, metformin, phenformin, metformin HCl and other salts thereof.

30. A pharmaceutical combination of Claim 29 wherein the other therapeutic agent is a biguanide and the compound of Claim 1 will be administered in a weight ratio to the biguanide within the range from about 0.001:1 to about 10:1.

31. A pharmaceutical combination of Claim 28 wherein the sulfonyl ureas are selected from glyburide, glibenclamide, glimepiride, glipizide, glyclazide, chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the beta-cells.
32. A pharmaceutical combination of Claim 31 wherein the combination of the compound of Claim 1 and the sulfonyl urea is administered in the same or separate oral dosage forms.

33. A pharmaceutical combination of Claim 28 wherein the glucosidase inhibitor is selected from acarbose and miglitol.

34. A pharmaceutical combination of Claim 33 wherein the combination of the compound of Claim 1 and the glucosidase inhibitor is administered in the same or separate oral dosage forms.

35. A pharmaceutical combination of Claim 28 wherein the PPAR γ agonist is a thiazolidinedione oral anti-diabetic agent.

36. A pharmaceutical combination of Claim 28 wherein the insulin sensitizer is selected from rosiglitazone, pioglitazone, MCC-555, GL-262570, englitazone, darglitazone, isaglitazone; JTT-501, L-895645, R-119702, NN-2344, and YM-440.

37. A pharmaceutical combination of Claim 28 wherein the PPARα/γ dual agonists are selected from MK-767/KRP-297, tesaglitazar and muraglitazar.

38. A pharmaceutical combination of Claim 25 wherein the hypolipidemic agent is an HMG CoA reductase inhibitor selected from mevastatin; compounds related to mevastatin; lovastatin; mevinolin; compounds related to lovastatin and mevinolin; pravastatin and compounds related to pravastatin; simvastatin and compounds related to simvastatin; fluvastatin; cerivastatin; atorvastatin; pitavastatin; nisvastatin; itavastatin; rosuvastatin; visastatin; compounds related to rosuvastatin and visastatin; pyrazole analogs of mevalonolactone derivatives; indene analogs of mevalonolactone derivatives; 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof; SC-45555; 3-substituted pentanedioic acid derivative; dichloroacetate; imidazole analogs of mevalonolactone; 3-carboxy-2-hydroxy-
propane-phosphonic acid derivatives; 2,3-disubstituted pyrrole, furan and thiophene
derivatives; naphthyl analogs of mevalonolactone; octahydranaphthalenes; keto
analogs of lovastatin and mevinolin; quinoline and pyridine derivatives; and
phosphinic acid compounds.

39. A pharmaceutical combination of Claim 25 wherein the hypolipidemic
agent is a squalene synthetase inhibitor selected from α-phosphono-sulfonates;
isoprenoid (phosphinyl-methyl) phosphonates; terpenoid pyrophosphates; farnesyl
diphosphate analog \( \Delta \) and presqualene pyrophosphate analogs;
phosphinylphosphonates; and cyclopropanes.

40. A pharmaceutical combination of Claim 25 wherein the hypolipidemic
agent is a fibric acid derivative selected from fenofibrate; gemfibrozil; clofibrate;
bezafibrate; ciprofibrate; clinofibrate; probucol; and compounds related to probucol.

41. A pharmaceutical combination of Claim 25 wherein the hypolipidemic
agent is a bile acid sequestrant selected from cholestyramine; colestipol; DEAE-
Sephadex; Secholex; Policexide; cholestagel; lipostabil; E-5050; N-substituted
ethanolamine derivatives; imanixil; tetrahydrolipstatin; 1stigmastanylphos-
phorylcholine; aminocyclodextrin; AJ-814; azulene derivatives; melinamide; 58-035;
CL-277,082; CL-283,546; disubstituted urea derivatives; nicotinic acid; niacin;
acipimox; acifran; neomycin; p-aminosalicylic acid; aspirin; poly(diallylmethylamine)
derivatives; quaternary amine poly(diallyldimethylammonium chloride; ionenes; and
other known serum cholesterol lowering agents.

42. A pharmaceutical combination of Claim 25 wherein the hypolipidemic
agent is an acyl CoA:cholesterol O-acyl transferase inhibitor selected from substituted
N-phenyl-N'-[1-phenylecyclopentyl]methyl]ureas; TS-962; F-1394; CS-505; F-12511;
HL-004; K-10085; and YIC-C8-434.

43. A pharmaceutical combination of Claim 25 wherein the hypolipidemic
agent is an upregulator of LDL receptor activity including MD-700.
44. A pharmaceutical combination of Claim 25 wherein the hypolipidemic agent is a cholesterol absorption inhibitor including ezetimibe.

45. A pharmaceutical combination of Claim 25 wherein the lipid-modulating agent is a cholesteryl transfer protein inhibitor selected from CP-529,414; SC-744; SC-795; CETi-1; and JTT-705.

46. A pharmaceutical combination of Claim 25 wherein the hypolipidemic agent is an ileal Na\(^+\)/bile acid cotransporter inhibitor.

47. A pharmaceutical combination of Claim 25 wherein the hypolipidemic agent is an ATP citrate lyase inhibitor.

48. A pharmaceutical combination of Claim 25 wherein the lipid-modulating agents are selected from a phytoestrogen compound selected from isolated soy bean protein, soy protein concentrate, soy flour, isoflavone, genistein, daidzein, glycine or equol, or phytosterols, phytostanol and tocotrienol; a beta-lactam cholesterol absorption inhibitor; an HDL upregulator selected from an LXR agonist, a PPAR \(\alpha\)-agonist and an FXR agonist; an LDI. catabolism promoter; a sodium-proton exchange inhibitor; an LDL-receptor inducer; steroidal glycoside; an anti-oxidant selected from beta-carotene, ascorbic acid, \(\alpha\)-tocopherol, retinol, Vitamin C antihomocysteine agent, folic acid, a folate, Vitamin B6, Vitamin B12 and Vitamin E; isoniazid; a cholesterol absorption inhibitor; an HMG-CoA synthase inhibitor; a lanosterol demethylase inhibitor; a PPAR \(\delta\) agonist for treating dyslipidemia; a sterol regulating element binding protein-I selected from a sphingolipid, ceramide, neutral sphingomyelenase or fragment thereof.

49. A pharmaceutical combination of Claim 25 wherein the hypolipidemic agent is selected from pravastatin; lovastatin; simvastatin; atorvastatin; fluvastatin; pitavastatin; rosuvastatin; niacin and cholestagel.
50. A pharmaceutical combination of Claim 25 wherein the anti-
hypertensive agents is selected from beta adrenergic blockers; L-type channel blockers
selected from diltiazem, verapamil, nifedipine, amlopidine and mybefradil; T-type
calcium channel blockers selected from diltiazem, verapamil, nifedipine, amlopidine
and mybefradil; diuretics selected from chlorothiazide, hydrochlorothiazide,
flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide,
trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricynafen,
chlorothalidone, furosemide, musolimine, bumetanide, triamtenene, amiloride and
spironolactone; renin inhibitors; ACE inhibitors selected from captopril, zofenopril,
fosinopril, enalapril, ceranopril, ciiazopril, delapril, pentopril, quinapril, ramipril and
lisinopril; AT-1 receptor antagonists selected from losartan, irbesartan and valsartan;
ET receptor antagonists selected from sitaxsentan and atrasentan; Dual ET/AII
antagonists; neutral endopeptidase inhibitors; vasopressinase inhibitors and dual NEP-
ACE inhibitors selected from omapatrilat and gemopatrilat; and nitrates.

51. A pharmaceutical combination of Claim 25 wherein the agent used to
treat sleep disorders is selected from melatonin analogs; melatonin receptor
antagonists; ML 1 B agonists; GABA receptor modulators; NMDA receptor-
modulators; histamine-3 (H3)receptor modulators; dopamine agonists and orexin
receptor modulators.

52. A pharmaceutical combination of Claim 25 wherein the agent used to
treat substance abuse and addictive disorders is selected from selective serotonin
reuptake inhibitors; methadone; buprenorphine; nicotine; and bupropion.

53. A pharmaceutical combination of Claim 25 wherein the anti-anxiety
agent is selected from benzodiazepines selected from diazepam, lorazepam,
oxazepam, alprazolam, chlordiazepoxide, clonazepam, chlorazepate, halazepam and
prazepam; 5HT1A receptor agonists selected from buspirone, flesinoxan, gepirone
and ipsapirone; and corticotropin releasing factor antagonists.
54. A pharmaceutical combination of Claim 25 wherein the anti-depressant agent is selected from norepinephrine reuptake inhibitors selected from tertiary and secondary amine tricyclics; selective serotonin reuptake inhibitors selected from fluoxetine, fluvoxamine, paroxetine and sertraline; monoamine oxidase inhibitors selected from isocarboxazid, phenelzine, tranylcypromine and selegiline; reversible inhibitors of monoamine oxidase including moclobemide; serotonin and norepinephrine reuptake inhibitors including venlafaxine; corticotropin releasing factor receptor antagonists; alpha-adrenoreceptor antagonists; and atypical antidepressants selected from bupropion, lithium, nefazodone, trazodone and viloxazine.

55. A pharmaceutical combination of Claim 25 wherein the anti-psychotic agent is selected from phenothiazine selected from chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine and trifluoperazine; thioxanthine selected from chlorprothixene and thiothixene; heterocyclic dibenzazepine selected from clozapine, olanzapine and aripiprazole; butyrophenone, including haloperidol; dipheyybutylpiperidine, including pimozide; indolone and molindolone classes of anti-psychotic agents; loxapine; sulpiride; risperidone; dopamine receptor antagonists; muscarinic receptor agonists; 5HT2A receptor antagonists, 5HT2A/dopamine receptor antagonists and partial agonists selected from olanzepine, aripiprazole, risperidone and ziprasidone.

56. A pharmaceutical combination of Claim 25 wherein the cognition-enhancing agent is selected from acetylcholinesterase inhibitors, including tacrine; muscarinic receptor-1 agonists, including milameline; nicotinic agonists; glutamic acid receptor modulators; and nootropic agents selected from piracetam and levetiracetam.

57. A pharmaceutical combination of Claim 25 wherein the agent used to treat Alzheimer’s disease and the agent used to treat cognitive disorders are selected from donepezil; tacrine; revastigaine; 5HT6; gamma secretase inhibitors; beta secretase inhibitors; SK channel blockers; Maxi-K blockers; and KCNQs blockers.
58. A pharmaceutical combination of Claim 25 wherein the agent used to treat Parkinson's disease is selected from levodopa with or without a COMT inhibitor; antiglutamatergic drugs selected from amantadine and riluzole; alpha-2 adrenergic antagonists including idazoxan; opiate antagonists including naltrexone; other dopamine agonists and transportor modulators including ropinirole; and pramipexole or neurotrophic factors including glial derived neurotrophic factor.

59. A pharmaceutical combination of Claim 25 wherein the anti-inflammatory agent is selected from prednisone; dexamethasone; cyclooxygenase inhibitors including COX-1 and COX-2 inhibitors selected from NSAID's, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen, Celebrex and Vioxx; CTLA4-Ig agonists and antagonists; CD40 ligand antagonists; IMPDH inhibitors including mycophenolate; integrin antagonists; alpha-4 beta-7 integrin antagonists; cell adhesion inhibitors; interferon gamma antagonists; ICAM-1; tumor necrosis factor antagonists selected from infliximab, OR1384, TNF-alpha inhibitors including tenidap, anti-TNF antibodies or soluble TNF receptors including etanercept; rapamycin selected from sirolimus and Rapamune; efalizumab; prostaglandin synthesis inhibitors; budesonide; clofazimine; CNI-1493; CD4 antagonists including priliximab; p38 mitogen-activated protein kinase inhibitors; protein tyrosine kinase inhibitors; IKK inhibitors; and agents for treatment of irritable bowel syndrome selected from Zelnorm and Maxi-K openers.

60. A pharmaceutical combination of Claim 25 wherein the other therapeutic agent is selected from cyclosporins; cyclosporin A; anti-IL-2 receptor; anti-CD45RB; anti-CD2; anti-CD3 (OKT-3); anti-CD4; anti-CD80; anti-CD86; monoclonal antibody OKT3; agents blocking the interaction between CD40 and gp39; antibodies specific for CD40 and/or gp39; CD154; fusion proteins constructed from CD40 and gp39; CD40lg; CD8gp39; nuclear translocation inhibitors of NF-kappa B function; deoxyspergualin; gold compounds; antiproliferative agents selected from methotrexate, FK506, tacrolimus, Prograf and mycophenolate mofetil; cytotoxic drugs selected from azathiprine and cyclophosphamide; anti-cytokines selected from anti-IL-4...
or IL-4 receptor fusion proteins; PDE 4 inhibitors including Ariflo and PTK inhibitors.

61. The method according to Claim 24, wherein the diseases or disorders are associated with the activity of the CB-1 receptor.

62. The method according to Claim 61, wherein the diseases or disorders are bulimia, obesity or any disease resulting in the patient becoming overweight.

63. The method according to Claim 61, wherein the diseases or disorders are metabolic disorders, eating disorders and appetite disorders, including treatment of the conditions associated with those disorders, such as obesity, diabetes, arteriosclerosis, hypertension, polycystic ovary disease, cardiovascular disease, osteoarthritis, dermatological disorders, hypertension, insulin resistance, hypercholesterolemia, hypertriglyceridemia, cholelithiasis and sleep disorders, hyperlipidemic conditions, bulimia nervosa and compulsive eating disorders.

64. The method according to Claim 61, wherein the diseases or disorders are obesity due to genetic or environmental causes, including overeating and bulimia, polycystic ovary disease, craniopharyngeoma, Prader-Willi Syndrome, Frohlich’s Syndrome, Type II diabetes, growth hormone deficiency, Turner’s Syndrome and other pathological states characterized by reduced metabolic activity or reduced energy expenditure.

65. The method according to Claim 61, wherein the diseases or disorders are psychiatric disorders selected from substance abuse, addictive disorders, depression, anxiety, mania and schizophrenia.

66. A method for the improvement of cognitive function and memory impairment, including the treatment of diseases selected from dementia, Alzheimer’s disease, short term memory loss and attention deficit disorders; neurodegenerative disorders, Parkinson’s Disease, cerebral apoplexy and craniocerebral trauma;
hypotension, hemorrhagic and endotoxin-induced hypotension; Parkinson's disease; Huntington's disease; Pick's disease; Creutzfeld-Jakob disease; head trauma; and age-related cognitive decline, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 24.

67. A method for the treatment of diseases associated with dysfunction of brain dopaminergic systems including Parkinson's Disease and substance abuse disorders, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 24.

68. A method for the treatment of diseases selected from catabolism in connection with pulmonary dysfunction and ventilator dependency; cardiac dysfunction, valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure; transplant rejection; rheumatoid arthritis; multiple sclerosis; inflammatory bowel disease; lupus; graft vs. host disease; T-cell mediated hypersensitivity disease; psoriasis; asthma; Hashimoto's thyroiditis; Guillain-Barre syndrome; cancer; contact dermatitis; allergic rhinitis; and ischemic or reperfusion injury, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 24.

69. A method for the treatment of substance abuse or dependence disorders in which substances of abuse or dependence include alcohol, amphetamines, amphetamine-like substances, caffeine, cannabis, cocaine, hallucinogens, inhalants, nicotine, opioids, phencyclidine, phencyclidine-like compounds, sedative-hypnotics, benzodiazepines, other known or unknown substances, or combinations of the substances of abuse, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 24.

70. The method according to Claim 69 wherein the substance abuse or dependence may occur without physiological dependence.
71. A method of treatment of drug or alcohol withdrawal syndromes and substance-induced anxiety or mood disorder with onset during withdrawal, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 24.

72. A method for the treatment of leukocyte activation-associated disorders including rejection due to organ transplant, acute transplant, xenotransplant, heterograft and homograft; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; rheumatoid arthritis, psoriatic arthritis and osteoarthritis; multiple sclerosis; chronic obstructive pulmonary disease (COPD), emphysema, bronchitis, and acute respiratory distress syndrome (ARDS); inflammatory bowel disease, ulcerative colitis and Crohn's disease; systemic lupus erythematosus; graft vs. host disease; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, gluten-sensitive enteropathy and Celiac disease; psoriasis; contact dermatitis; Hashimoto's thyroiditis; Sjogren's syndrome; autoimmune hyperthyroidism, such as Graves' Disease; Addison's disease; autoimmune polyglandular disease or syndrome; autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituitarism; Guillain-Barre syndrome; other autoimmune diseases; glomerulonephritis; serum sickness; urticaria; asthma, hayfever, allergic rhinitis and skin allergies; scleroderma; mycosis fungoides; acute inflammatory and respiratory responses, including acute respiratory distress syndrome and ischemia/reperfusion injury; dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplantaris; Pyoderma gangrenosum; Sezary's syndrome; atopic dermatitis; systemic sclerosis; and morphea, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 24.

73. A method for the treatment of inflammatory diseases, including arthritis, inflammatory bowel disease and autoimmune glomerulonephritis, which
comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 24.
C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search: 14 April 2005

Date of mailing of the international search report: 25/04/2005

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