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

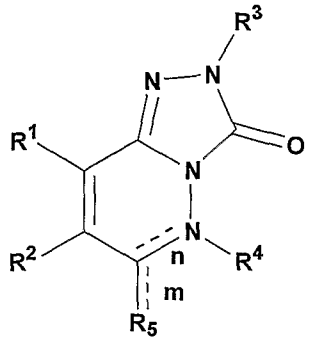
Delta-9-tetrahydrocannabinol or Delta-9 THC, the principle active component of Cannabis sativa (marijuana), is a member of a large family of lipophilic compounds (i.e., cannabinoids) that mediate physiological and psychotropic effects including regulation of appetite, immunosuppression, analgesia, inflammation, emesis, anti-nocioception, 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., *Pyschopharm.*, 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



I

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.

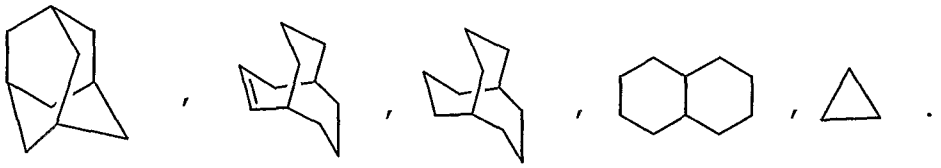
As used herein, the term "alkyl" denotes branched or unbranched hydrocarbon chains containing 1 to 20 carbons, preferably 1 to 12 carbons, and more preferably 1 to 8 carbons, in the normal chain, such as, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, hexyl, isohexyl, 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, heterocyclyl, aryl, heteroaryl, carboxyl, carbalkoyl, carboxamido, carbonyl, alkenyl, alkynyl, nitro, amino, alkoxy, aryloxy, arylalkyloxy, heteroaryloxy, amido, $-OC(O)NR^8R^9$, $-OC(O)R^8$, $-OPO_3H$, $-OSO_3H$, 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-nonenyl, 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, arylcarbonylamino, 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-butynyl, 2-butynyl, 4-pentynyl, 3-

pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,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,

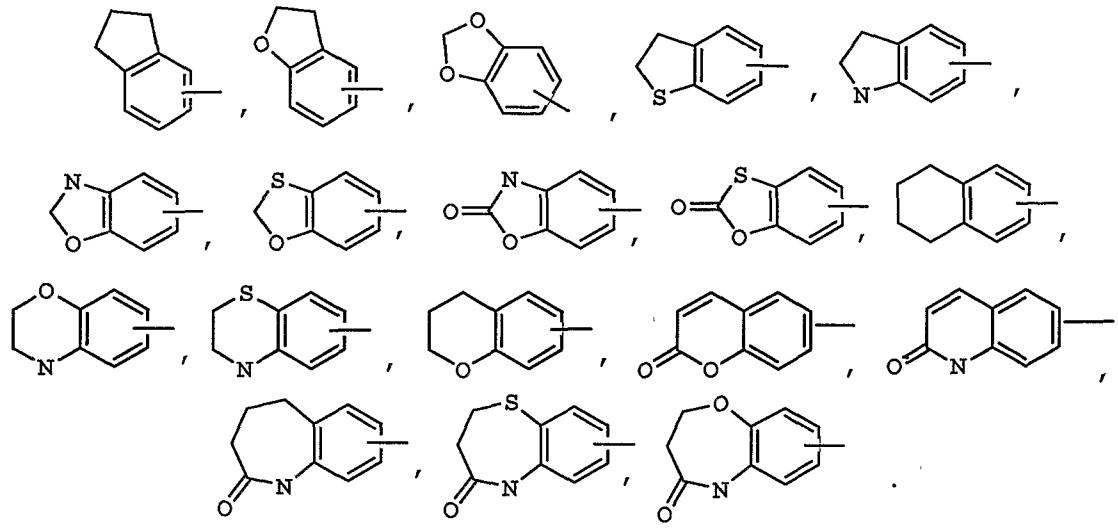


Further, any cycloalkyl may be optionally substituted through any available carbon atoms with one or more groups selected from hydrogen, halo, haloalkyl, alkyl, alkoxy, haloalkyloxy, hydroxyl, alkenyl, alkynyl, aryl, aryloxy, heteroaryl, heteroaryloxy, arylalkyl, heteroarylalkyl, alkylamido, alkanoylamino, 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-

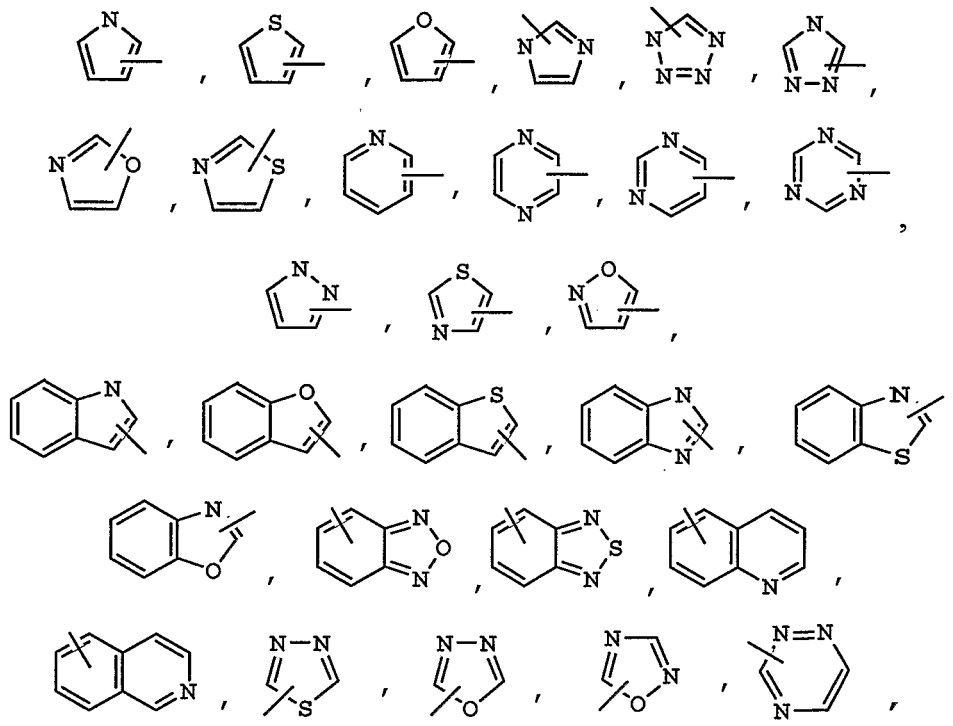
naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring, for example



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, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, 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, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl 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 Press, New York, NY; and Katritzky, A. R., Rees, C. W., Scriven, E. F., eds.

Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982-1995 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", "heterocyclyl" 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, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl,

azepinyl, pyrrolyl, pyrrolidinyl, furanyl, thienyl, pyrazolyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isooxazolyl, isoxazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, thiadiazolyl, tetrahydropyranyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, oxadiazolyl and other heterocycles described in Katritzky, A. R. and Rees, C. W., eds. *Comprehensive Heterocyclic Chemistry: The Structure, Reactions, Synthesis and Uses of Heterocyclic Compounds* 1984, Pergamon Press, New York, NY; and Katritzky, A. R., Rees, C. W., Scriven, E. F., eds. *Comprehensive Heterocyclic Chemistry II: A Review of the Literature 1982-1995* 1996, Elsevier Science, Inc., Tarrytown, NY; and references therein.

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 "arylalkyl", "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 arylalkyl 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 "methylene," as used herein, refers to a $-CH_2-$ group.

The term "nitro," as used herein, refers to a $-NO_2$ group.

The compounds of formula I can be present as salts, which are also within the scope of this invention. Pharmaceutically 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 (C_1-C_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 $-PO_3H_2$ 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 alkyoxymethyl-, acyloxymethyl-, phosphoryloxymethyl-, or sulfonyloxymethyl-groups. Alkylation of amines of formula I may result in the generation of quarternary 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 1.

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 methyleneoxy-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);

A Textbook of Drug Design and Development, P. Krogsgaard–Larson and H. Bundgaard, eds. Ch 5, pgs 113-191 (Harwood Academic Publishers, 1991).

Hydrolysis in Drug and Prodrug Metabolism, B. Testa and J. M. Mayer, (Verlag Helvetica Chimica Acta AG, Zurich, Switzerland; Wiley-VCH, Weinheim, Federal Republic of Germany, 2003)

Ettmayer, P.; Amidon, G. L.; Clement, B.; Testa, B. "Lessons Learned from Marketed and Investigational Prodrugs" *J. Med. Chem.* 2004, *47 (10)*, 2393-2404.

Davidsen, S. K. et al. "N-(Acyloxyalkyl)pyridinium Salts as Soluble Prodrugs of a Potent Platelet Activating Factor Antagonist" *J. Med. Chem.* 1994, *37 (26)*, 4423-4429.

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

Et_3N = triethylamine

Et_2O = diethyl ether

HOBt = 1-hydroxybenzotriazole hydrate

HPLC = high performance liquid chromatography

LAH = lithium aluminum hydride

LC/MS = high performace 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)

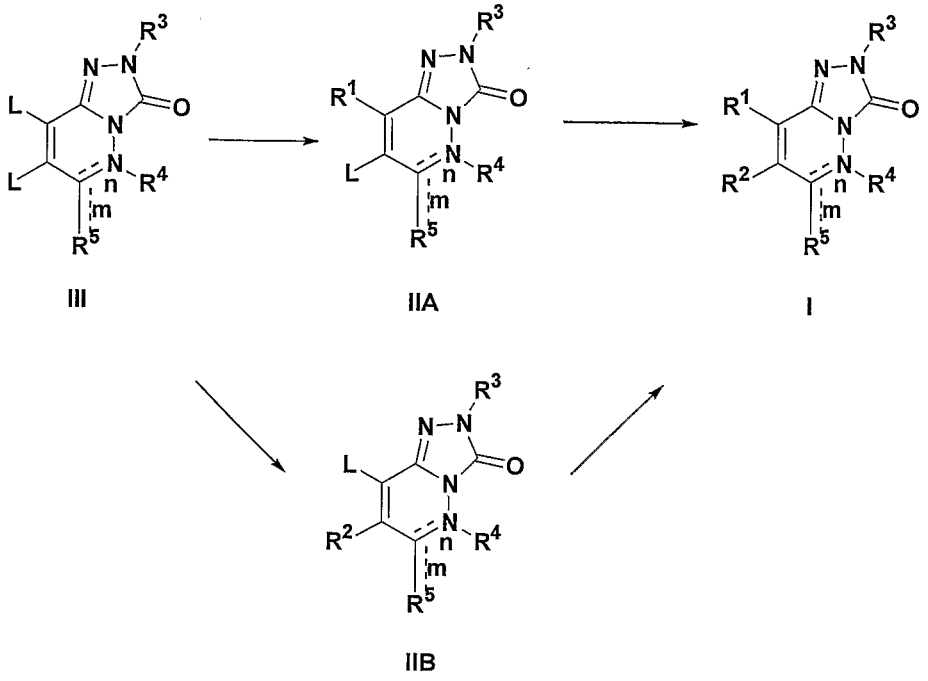
nM = nanomolar

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, R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9 are as described for a compound of formula **I**.

SCHEME I

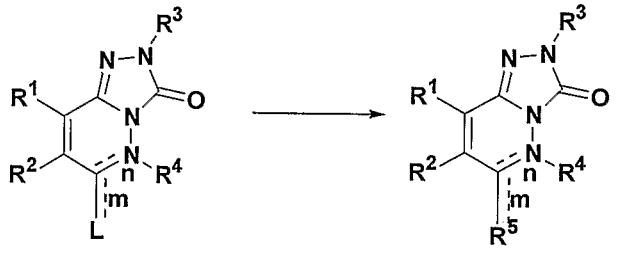


III IIA I

IIB

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 , R^1-L or R^2-L gives compounds of formula II that can be further reacted under similar conditions to give compounds of formula I.

SCHEME II

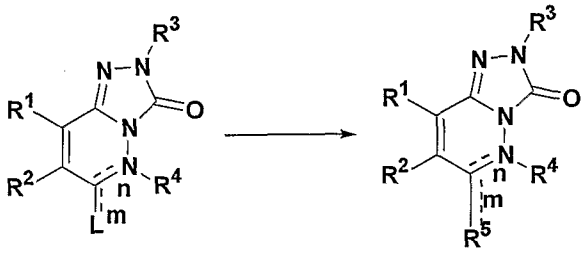


IV I

Compounds of formula I of the invention where R^5 is $-OR^6$, $-NR^8R^9$, or $-NR^8S(O)_pR^9$ may be prepared as depicted in Scheme II by coupling compounds of formula IV wherein L represents a leaving group, such as chlorine, fluorine, trifluorosulfonyloxy- and the like, with R^5-M or a suitable precursor to R^5-M known to those skilled in the art where M is hydrogen or metalloid, such as boron, tin, zinc, copper, potassium, sodium and the like. This coupling may optionally be facilitated by catalysts such as Pd(0), Cu(I) and the like. Examples of these transformations can be found herein and in: Wagaw, S. and Buchwald, S.L., *J. Org. Chem.*, 1996, *61(21)*, 7240-7241; Konno, S. et al., *Chem. Pharm. Bull.*, 1982, *30(1)*, 152-157; Abdel-Rahman, R.M. and Ghareib, M., *Indian J. Chem.*, 1987, *26B*, 496-500; Saad, H.A. et al., *Indian J. Chem.*, 1998, *37B*, 1142-1148; Wolfe, J.P. et al., *Acc. Chem. Res.*, 1998, *31(12)*, 805-818; Wolfe, J.P. et al., *J. Org. Chem.*, 2000, *65(4)*, 1158-1174; Hartwig, J.F., *Acc. Chem. Res.*, 1998, *31(12)*, 852-860; Alonso, D.A. et al., *J. Org. Chem.*, 2002, *67(46)*, 5588-5594; Miyaura, N. and Suzuki, A., *Chem. Rev.*, 1995, *95(7)*, 2457-2483; Littke, A.F. et al., *J. Am. Chem. Soc.*, 2000, *122(17)*, 4020-4028; Nishimura, M. et al., *Tetrahedron*, 2002, *58*, 5779-5787; Miller, J.A. and Farrell, R.P., *Tetrahedron Lett.*, 1998, *39(40)*, 7275-7278; Mitchell, T.N., *Synthesis*, 1992*(9)*, 803-815; Sato, N. and Narita, N., *Synthesis*, 2001*(10)*, 1551-1555; Nannini, G. et al., *Eur. J. Med. Chem.-Chimica Therapeutica*, 1979, *14(1)*, 53-60; Matsuda, T. et al., *Bioorg. Med. Chem. Lett.*, 2001*(11)*, 2369-2372; Konno, S. et al., *Chem. Pharm. Bull.*, 1982, *30(1)*, 152-157; Sato, N. and Narita, N., *Synthesis*, 2001*(10)*, 1551-1555; and references therein.

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_2CO_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 phenylsulfonylchloride, $Cl\text{-}S(O)_pR^9$ and the like, or an acylating reagent such as acetyl chloride, methylchloroformate, and the like, to form compounds of formula I wherein n denotes a double bond and m denotes a single bond.

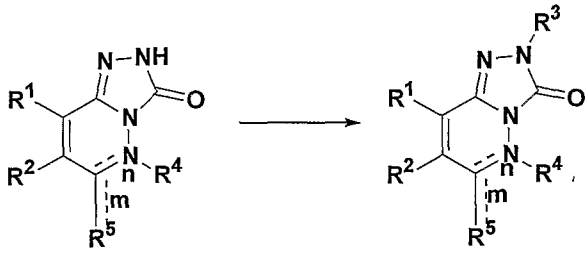
SCHEME III



V I

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.

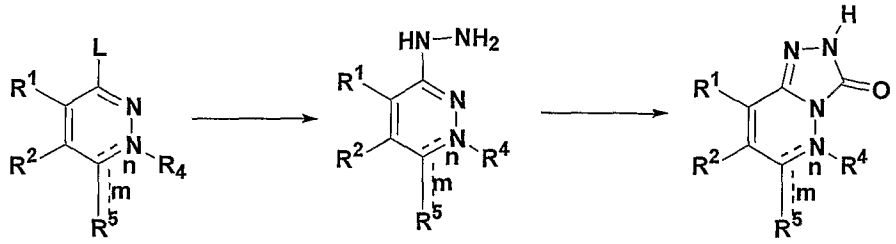
SCHEME IV



VI I

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.

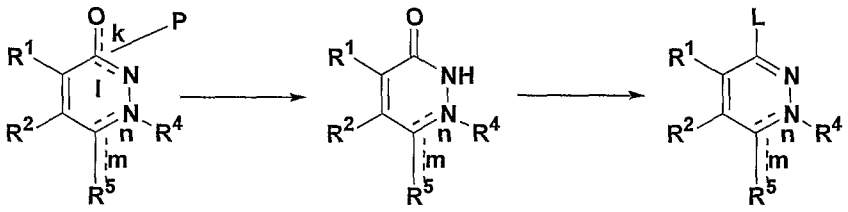
SCHEME V



VIII VII VI

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-diimidazole, phosgene, and the like to give compounds of formula VI.

SCHEME VI



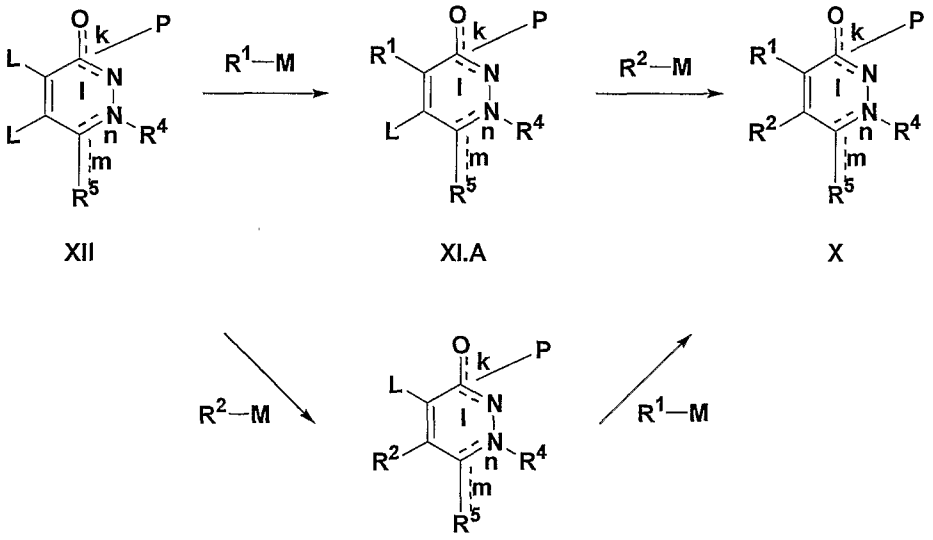
X IX VIII

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 $AlCl_3$ 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



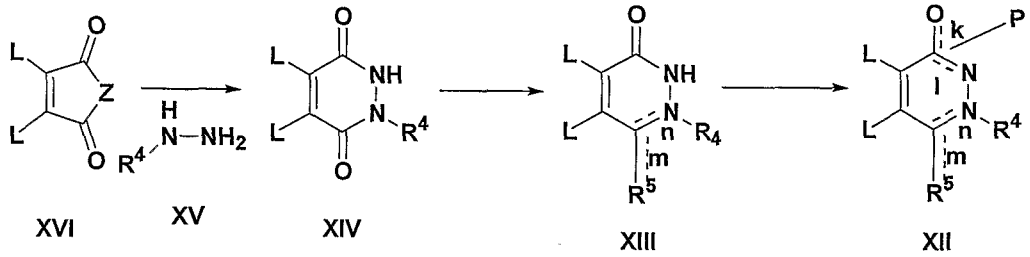
XII XI.A X

XI.B

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. Examples of such transformations may be found herein and in: Matyus, P. et al. *Synlett* 2004, *(7)*, 1123-1139; Miyaura, N., Suzuki, A. *Chem. Rev.* 1995, *95*, 2457-2483; Karmas, G. and Spoerri, P.E., *J. Am. Chem. Soc.*, 1956, *78(10)*, 2141-2144; Matsuda, T. et al. *Bioorg. Med. Chem. Lett.*, 2001*(11)*, 2369-2372; Konno, S. et al.,

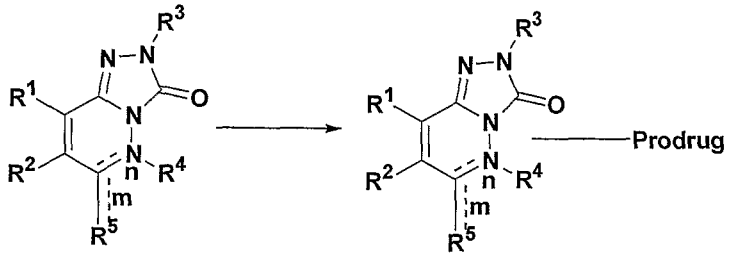
Chem. Pharm. Bull., 1982, *30(1)*, 152-157; Akita, Y., Shimazaki, M. and Ohta, A., *Synthesis*, 1981*(12)*, 974-975; and references therein.

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: Chambers, R. D.; Musgrave, W. K. R.; Sargent, C. R. *J. Chem. Soc. Perkin I*, 1981, 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

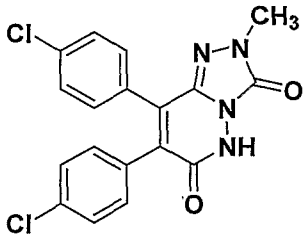
Flow rate: 4 ml/min

Solvent A: 0.2% phosphoric acid, 90% water, 10% methanol

Solvent B: 0.2% phosphoric acid, 90% methanol, 10% water

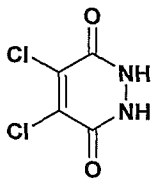
EXAMPLE 1

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



EXAMPLE 1A

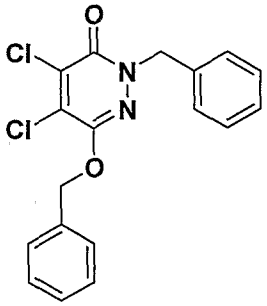
Preparation of 4,5-Dichloro-1,2-dihydropyridazine-3,6-dione



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 (66.6gm, 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 (65gm, 90% yield) as white solid. MS(M+1)=181.0

EXAMPLE 1B

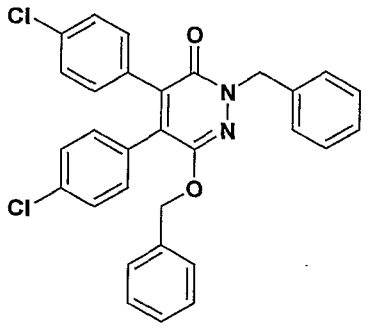
Preparation of 2-Benzyl-6-(benzyloxy)-4,5-dichloropyridazin-3(2H)-one



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, 88.56mmol). 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-(benzyloxy)-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

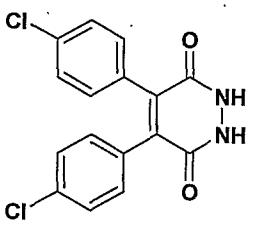
Preparation of 2-Benzyl-6-(benzyloxy)-4,5-bis(4-chlorophenyl)pyridazin-3(2H)-one



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 $Pd(PPh_3)_4$ (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($MgSO_4$), 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

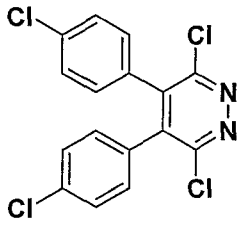


To a round bottom flask was added 2-benzyl-6-(benzyloxy)-4,5-bis(4-chlorophenyl)pyridazin-3(2H)-one (15.5 gm, 30.21 mmol), toluene(70 ml) and alumina chloride (10.08 gm, 75.54 mmol). The reaction was stirred at 90°C for 2 h. After this time, the reaction was cooled to 0°C and water (200 ml) was slowly 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 ($MgSO_4$), 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

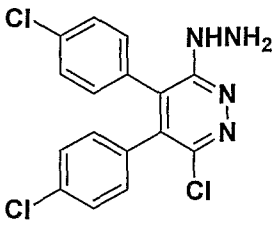
Preparation of 3,6-Dichloro-4,5-bis(4-chlorophenyl)pyridazine.



To the 4,5-bis(4-chlorophenyl)-1,2-dihydropyridazine-3,6-dione was added $POCl_3$ (50 ml), dropwise. The resultant reaction mixture was heated reflux for 2 h. The reaction turned into black. After this time, $POCl_3$ was removed under reduced pressure. To the reisude 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 CH_2Cl_2 (250 ml) and the solution was filtered through Celite(30 ml). Collect the filtrate and concentrate to give brown solid. The crude solid was recystallized from CH_2Cl_2 (30ml) 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

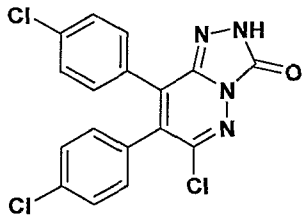


To a r.b. flask was added 3,5-dichloro-4,5-bis(4-chlorophenyl)pyridazine (4.5 gm, 12.2 mmol), pyridine (20 ml) and hydrazine monohydrate (1.494 gm, 30.49

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 (3.7gm, 83% yield) as a solid. MS (M+H)=364.9

EXAMPLE 1F

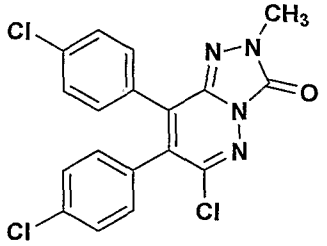
Preparation of 6-Chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one



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]triozolo[4,3-b]pyridazin-3(2H)-one to give the title compound 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; ^{1}HNMR (DMSO-D6) 7.39-7.44(m, 4H), 7.28(m, 4H).

EXAMPLE 1G

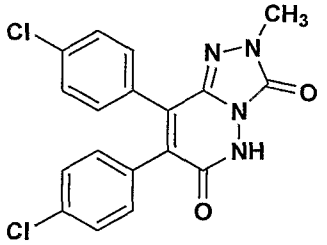
Preparation of 6-Chloro-7,8-bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one



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}HNMR(DMSO-D6) 7.42(m, 4H), 7.28(m, 4H), 3.56(s, 3H). ^{13}CNMR (DMSO-D6) 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

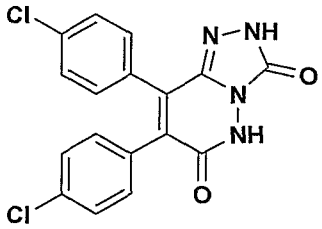


To a round bottom flask was added 7,8-bis(4-chlorophenyl)-2-methyl-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (1.2 gm, 3.29 mmol), THF (15 ml), and potassium trimethylsilanolate (1.7gm, 13.2 mmol). The reaction was refluxed for 2 hrs. The reaction was then cooled to RT, and the solution was concentrated 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 ^{1}HNMR (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

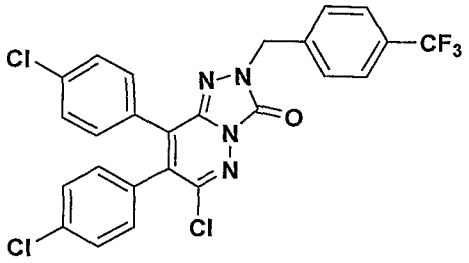
Preparation of 7,8-Bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione



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 trimethylsilanolate (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 ($MgSO_4$), 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

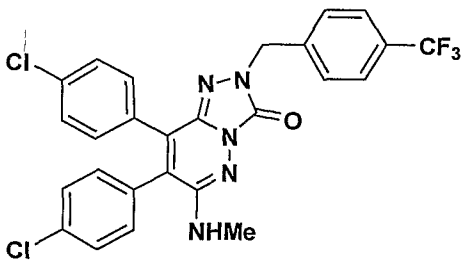
Preparation of 2-(4-(Trifluoromethyl)benzyl)-6-chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one



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 K_2CO_3 (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

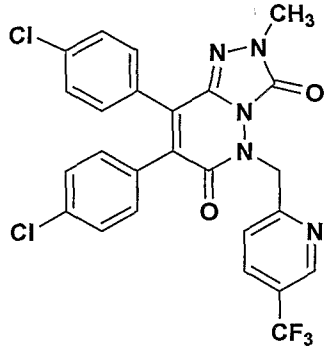


A mixture of 2-(4-(trifluoromethyl)benzyl)-6-chloro-7,8-bis(4-chlorophenyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one (50 mg, 0.091 mmol), prepared as described in Example 3, and 2.0 M methyl amine in THF (0.4 mL) was stirred at reflux for 12 h. After this time, the reaction mixture was cooled to RT 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 $MgSO_4$, 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; ^{1}H NMR ($CDCl_3$), 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).

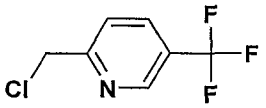
EXAMPLE 5

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



EXAMPLE5A

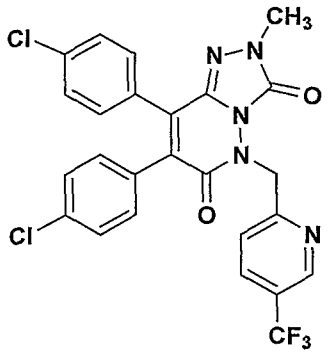
Preparation of 2-(Chloromethyl)-5-(trifluoromethyl)pyridine



The mixture of (5-(trifluoromethyl)pyridin-2-yl)methanol HCl salt (293mg, 1.4mmol) and $SOCl_2$(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

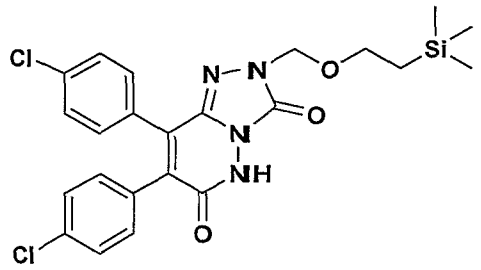
Preparation of 7,8-Bis(4-chlorophenyl)-2-methyl-5-((5-(trifluoromethyl)pyridin-2-yl)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione



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), K_2CO_3 (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 Na_2SO_4, 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-alylated 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; ^{1}H NMR ($CDCl_3$) 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).

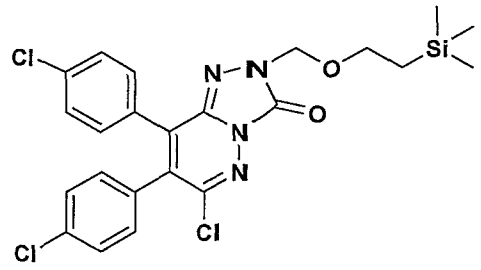
EXAMPLE 6

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

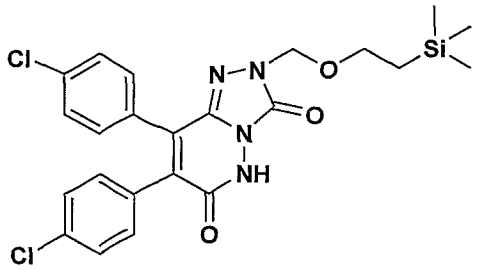
Preparation of 6-chloro-7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one



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 Na_2SO_4 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

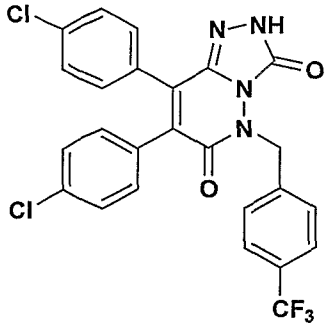
Preparation of 7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione



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 trimethylsilyloxide (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 Na_2SO_4, 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.

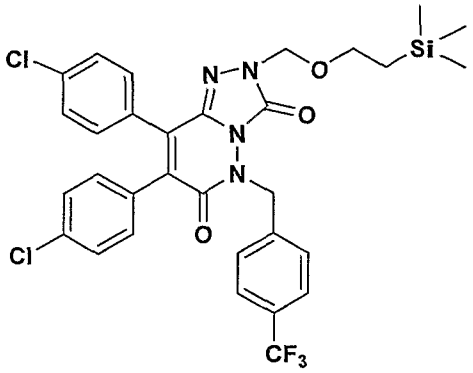
EXAMPLE 7

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

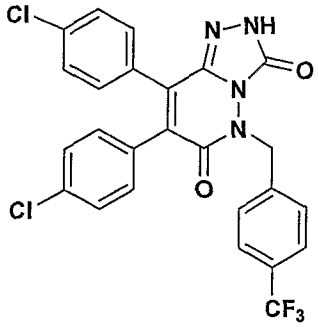
Preparation of 5-(4-(trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione



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), K_2CO_3 (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 Na_2SO_4, 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

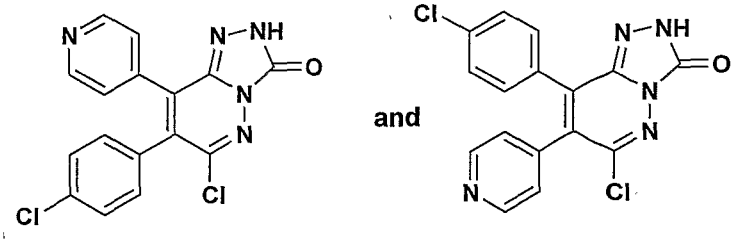


The solution of 5-(4-(trifluoromethyl)benzyl)-7,8-bis(4-chlorophenyl)-2-((2-(trimethylsilyl)ethoxy)methyl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (118mg, 0.18mmol) in 4M HCl in dioxane (4ml) in a sealed tube was heated at 90°C

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-(4-(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; ^{1}H (CDCl3) d 11.46(1H), 7.70(2H), 7.55(2H), 7.27(4H), 7.14(2H), 7.06(2H), 5.96(2H).

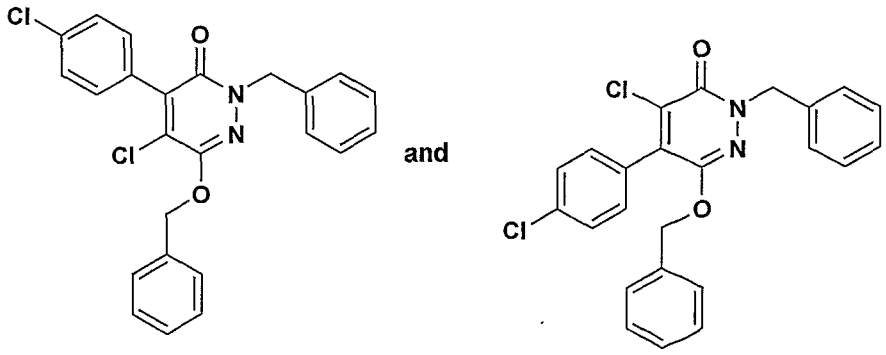
EXAMPLE 8

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-(benzyloxy)-5-chloro-4-(4-chlorophenyl)pyridazin-3(2H)-one and 2-Benzyl-6-(benzyloxy)-4-chloro-5-(4-chlorophenyl)pyridazin-3(2H)-one

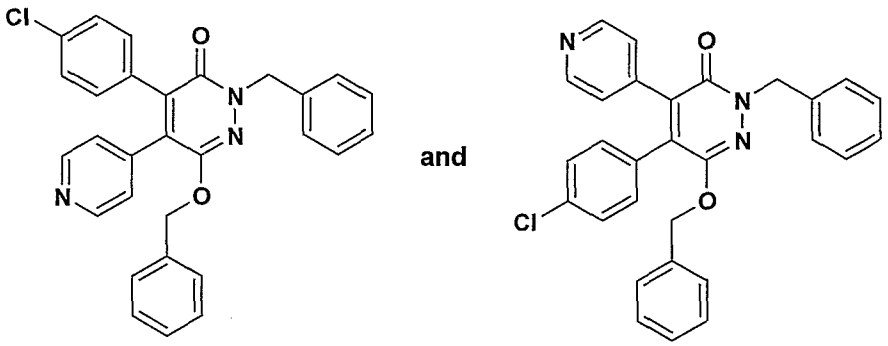


To a solution of 2-benzyl-6-(benzyloxy)-4,5-dichloropyridazin-3(2H)-one(11.8g, 32.7mmol), prepared as described in example 1B, in toluene (200ml) was added $Pd(PPh_3)_4$ (2.26g, 1.96mmol). After 5min, 2N aqueous sodium carbonate (65 ml, 130mmol) solution was added, followed by 4-chlorophenylboronic acid (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 Na_2SO_4, 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-(benzyloxy)-5-chloro-4-(4-chlorophenyl)pyridazin-3(2H)-one and 2-benzyl-6-(benzyloxy)-4-chloro-5-(4-chlorophenyl)pyridazin-3(2H)-one which were obtained as a mixture.

EXAMPLE 8B

Preparation 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

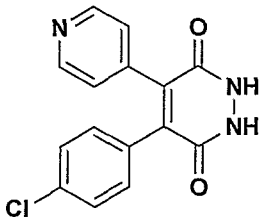


To a solution the mixture of 2-benzyl-6-(benzyloxy)-5-chloro-4-(4-chlorophenyl)pyridazin-3(2H)-one and 2-benzyl-6-(benzyloxy)-4-chloro-5-(4-chlorophenyl)pyridazin-3(2H)-one (9.9g, 22.7mmol), prepared as described in Example 8A, in toluene (136ml) was added $Pd(PPh_3)_4$ (2.35g, 1.17mmol). After 2min, 2N sodium carbonate (45.4 ml, 90.8mmol) solution was added, followed by 4-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-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 Na_2SO_4, 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-(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 as a mixture, as light yellow solid (4.5g, 29% two steps).

EXAMPLE 8C

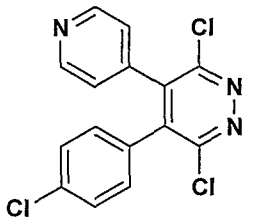
Preparation of 4-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,2-dihydropyridazine-3,6-dione



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 $AlCl_3$ (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

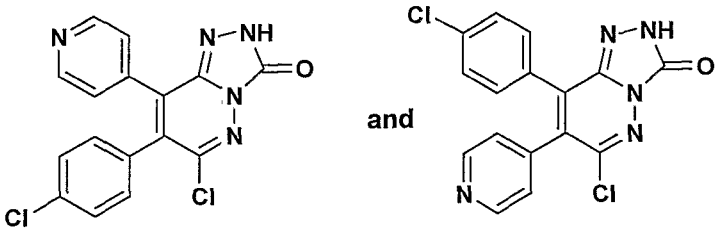


A sealed tube with of 4-(4-Chlorophenyl)-5-(pyridin-4-yl)-1,2-dihydropyridazine-3,6-dione (0.1g, 0.33mmol) and $POCl_3$(0.3ml, 3.2mmol) was stirred at 135°C in an oil bath for 1h. After this time, the solution was cooled to RT and poured into 1.5N NaOH-ice water (9.3ml, 14mmol). Ethyl acetate was added to the resultant solution. The organic layer was washed with saturated aqueous NaCl. The organic layer was dried over Na_2SO_4, 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

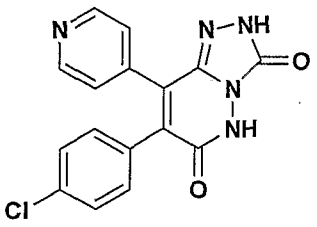
Preparation of 6-Chloro-7-(4-chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one and 6-Chloro-8-(4-chlorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazin-3(2H)-one



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 Na_2SO_4, 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 sold (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

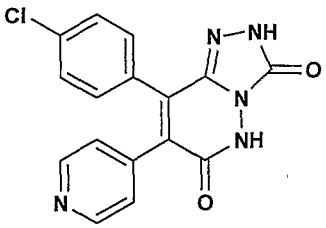
Preparation of 7-(4-Chlorophenyl)-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione



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 trimethylsilyloxide, 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

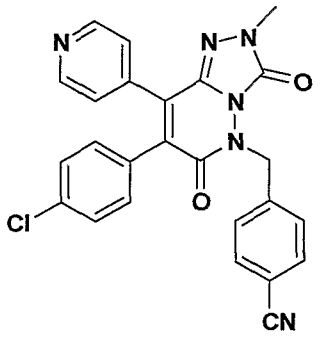
Preparation of 8-(4-chlorophenyl)-7-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione



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 trimethylsilyloxide, 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

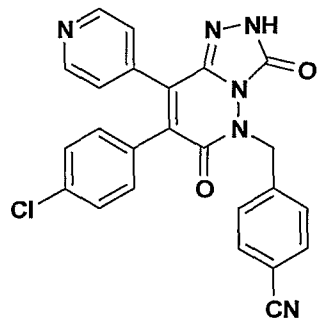
Preparation of 4-((7-(4-Chlorophenyl)-2-methyl-3,6-dioxo-8-(pyridin-4-yl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-5(6H)-yl)methyl)benzonitrile



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) , K_2CO_3(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 Na_2SO_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)-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; ^{1}H 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

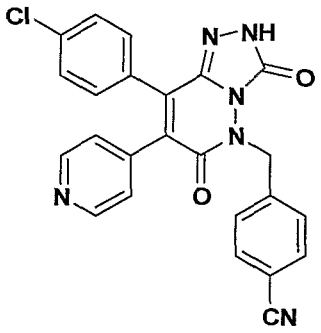
Preparation of 4-((7-(4-Chlorophenyl)-3,6-dioxo-8-(pyridin-4-yl)-2,3-dihydro-[1,2,4]triazolo[4,3-b]pyridazin-5(6H)-yl)methyl)benzonitrile



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_2CO_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_2SO_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]pyridazin-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]pyridazin-5(6H)-yl)methyl)benzonitrile

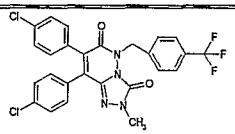
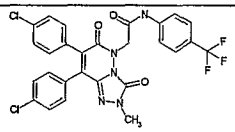
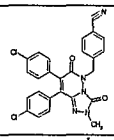
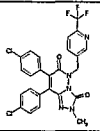
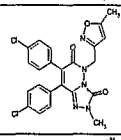
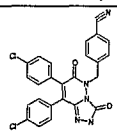
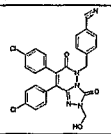
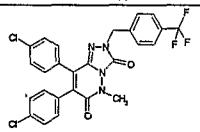
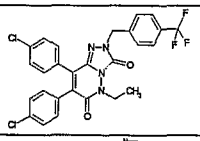
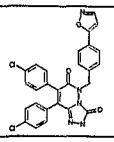


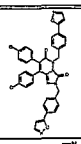
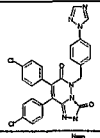
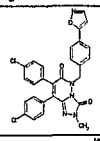
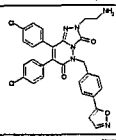
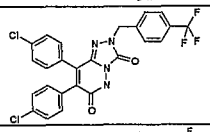
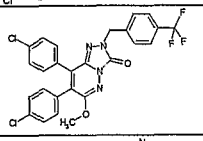
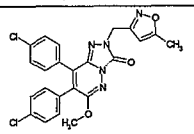
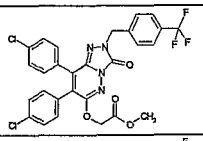
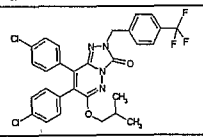
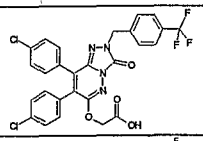
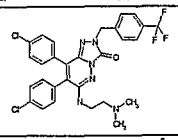
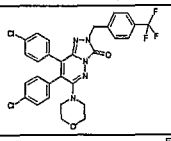
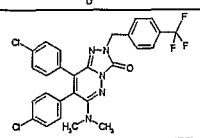
To the solution of 7-(4-chlorophenyl)-2-methyl-8-(pyridin-4-yl)-[1,2,4]triazolo[4,3-b]pyridazine-3,6(2H,5H)-dione (12mg, 0.034mmol), prepared as described in Example in DMF (0.5ml) was added K_2CO_3 (7mg, 0.05mmol) followed by 4-(bromomethyl)benzonitrile (8mg, 0.041mmol). After 15min, the reaction mixture was diluted with ethyl acetate. The resultant solution was washed with water. The organic layer was dried over Na_2SO_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]pyridazin-5(6H)-yl)methyl)benzonitrile, (3.5mg, 18%) as a mono

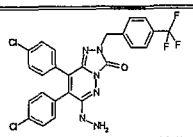
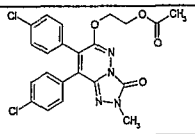
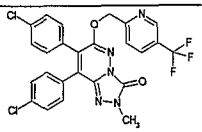
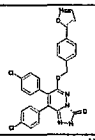
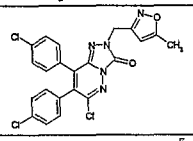
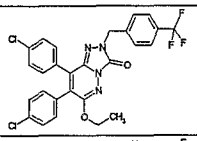
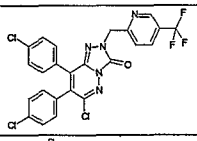
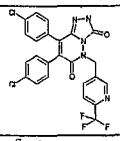
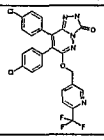
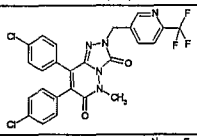
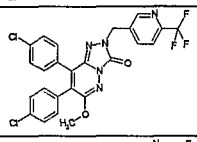
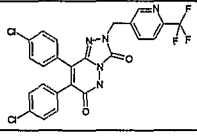
trifluoroacetate salt as a yellow foam. MS M+H=455. ^{1}H (CD_3OD) δ 8.66(2H), 7.71-7.65(6H), 7.34-7.31(4H), 5.93(2H).

EXAMPLES 14 TO 48

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

Example Number	Structure	HPLC Retention Time (min)	Mass Specs Observed (M+H)
14		4.21	545
15		4.21	588
16		3.58	502
17		3.94	546
18		3.66	482
19		3.76	488
20		3.72	518
21		4.19	545
22		4.27	559
23		3.85	528

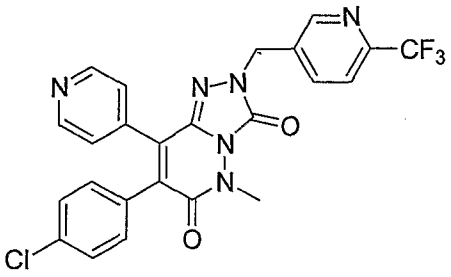
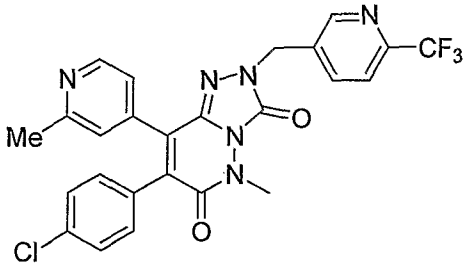
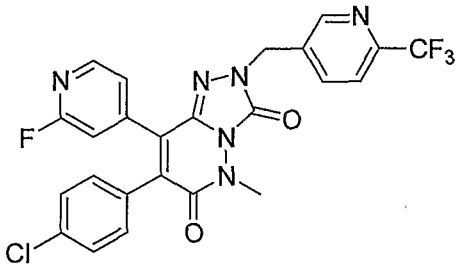
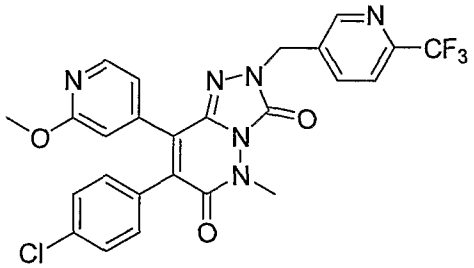
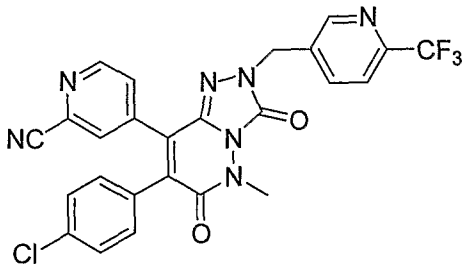
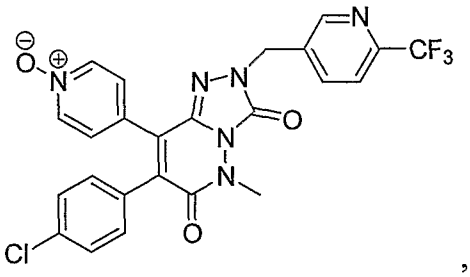
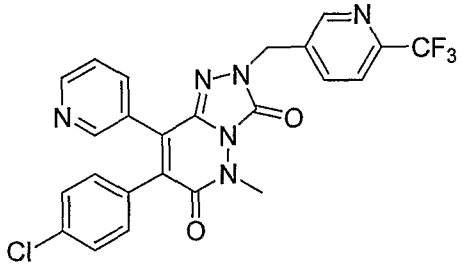
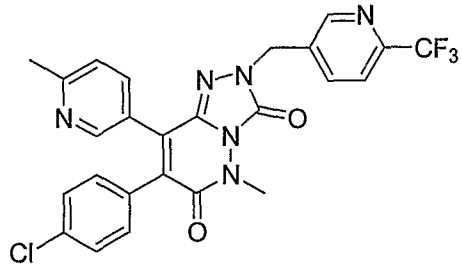
Example Number	Structure	HPLC Retention Time (min)	Mass Specs Observed (M+H)
24		4.1	687
25		3.67	530
26		3.9	544
27		2.98	573
28		4.23	531
29		4.27	545
30		3.86	482
31		4.24	603
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33		4.16	589
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35		4.23	600
36		4.29	558

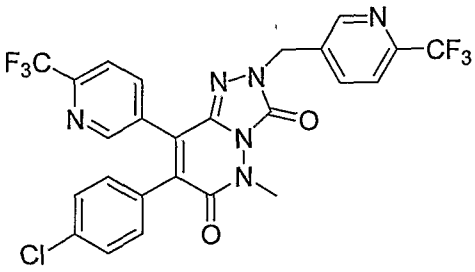
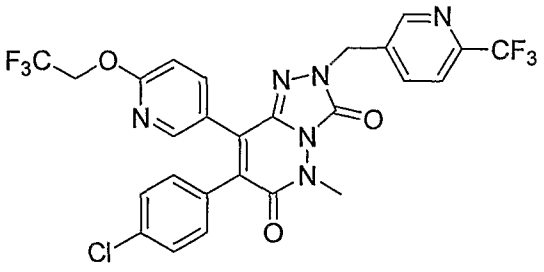
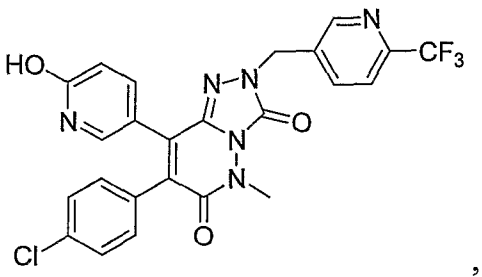
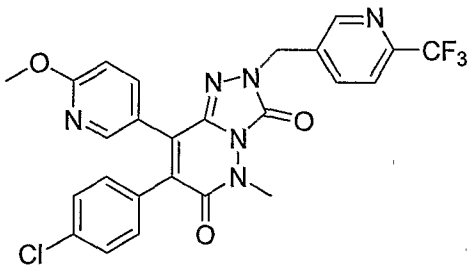
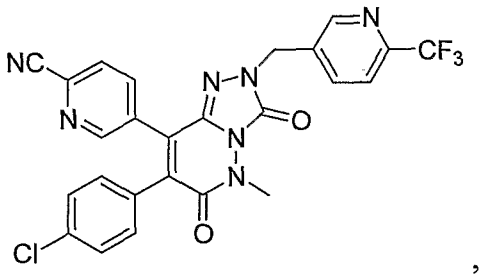
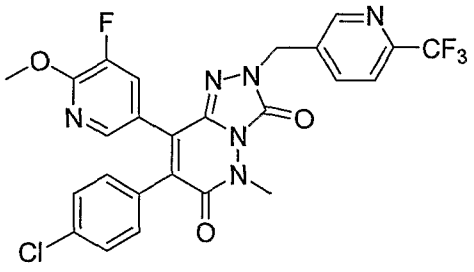
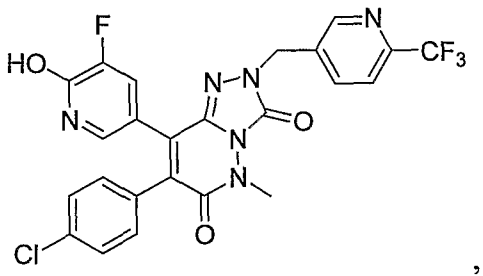
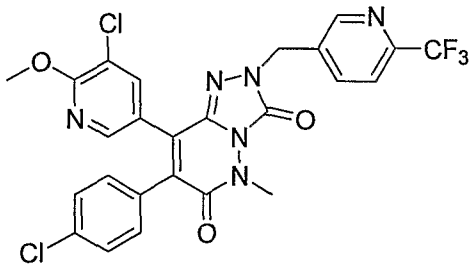
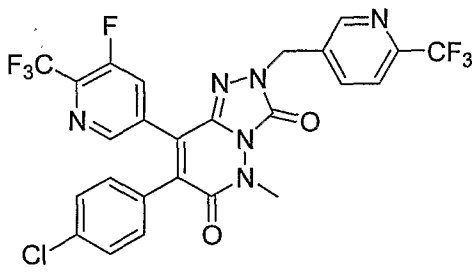
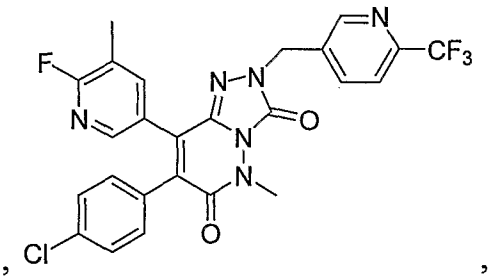
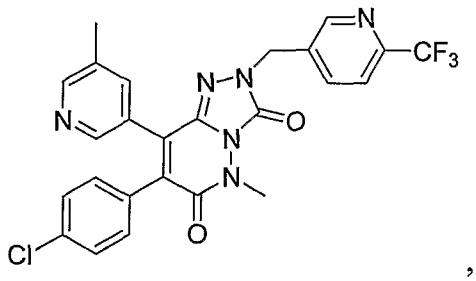
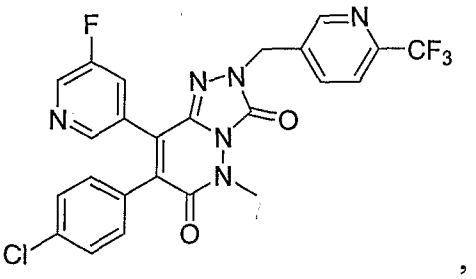
Example Number	Structure	HPLC Retention Time (min)	Mass Specs Observed (M+H)
37		3.59	545
38		3.74	473
39		4.12	546
40		3.95	530
41		3.82	486
42		4.36	559
43		4.06	550
44		3.61	532
45		3.72	532
46		3.66	546
47		3.79	546
48		3.76	532

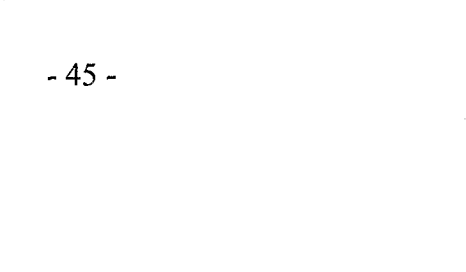
The compounds of Set A below, in which R^1 varies, R^2 is 4-chlorophenyl, R^3 is 2-(trifluoromethyl)pyridin-5-ylmethyl, R^4 is methyl, R^5 is O, n is single bond and m

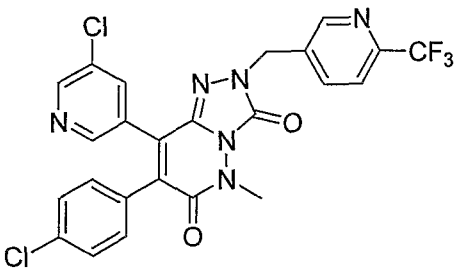
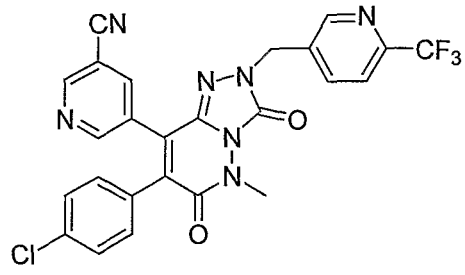
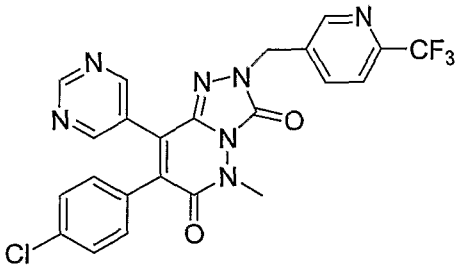
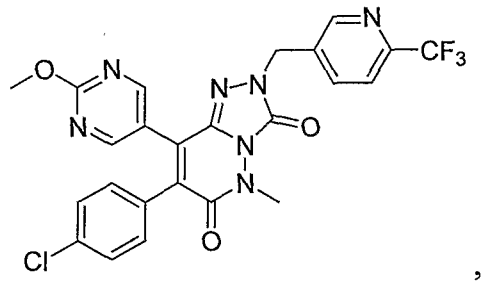
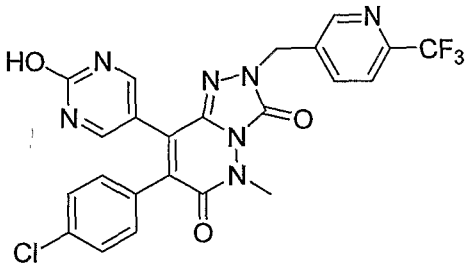
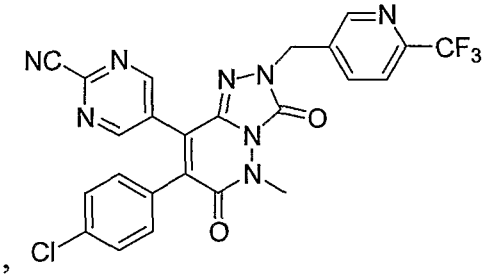
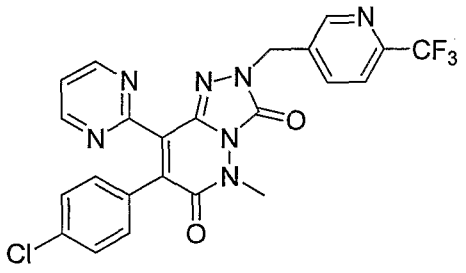
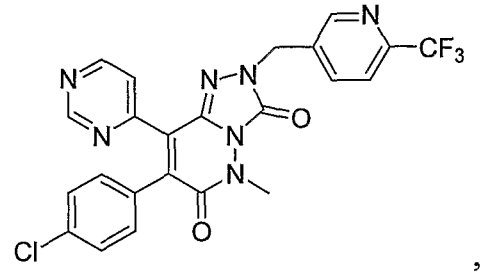
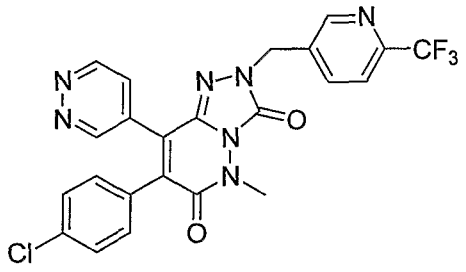
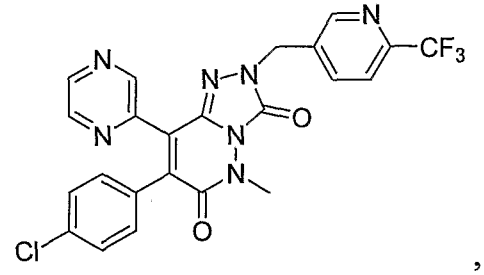
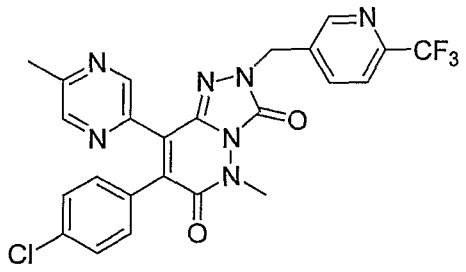
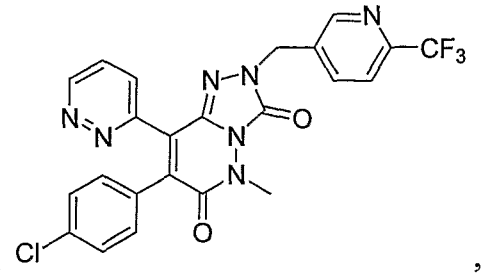
is double bond, may be prepared by one skilled in the art by the methods described above. Furthermore, the variations of R^1 demonstrated herein can be combined with R^2-R^9, n and m found in the working examples above. The compounds of Set A are meant to further illustrate the scope of the invention without being limiting in any way.

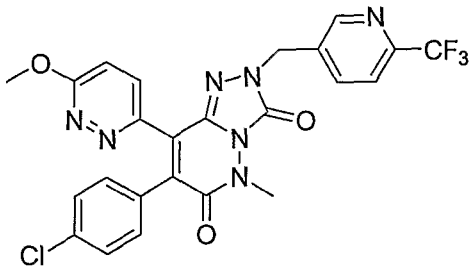
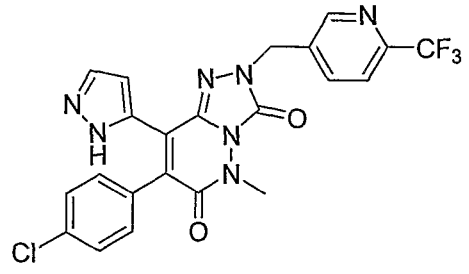
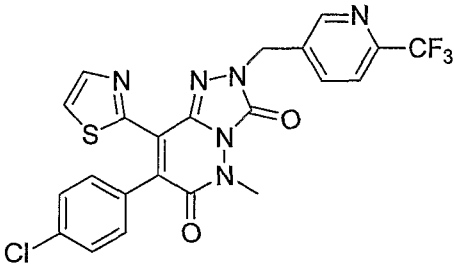
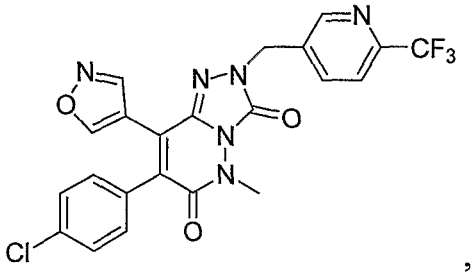
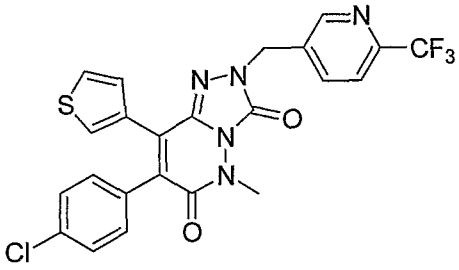
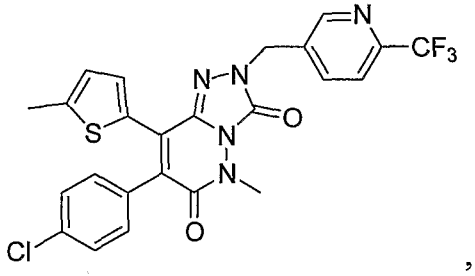
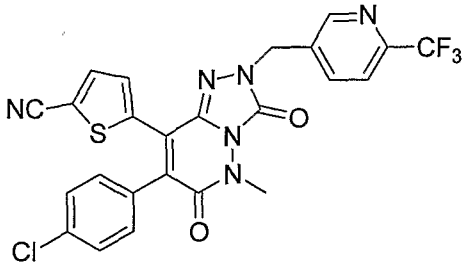
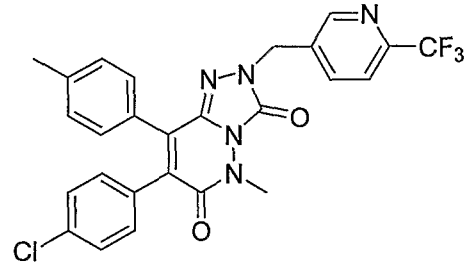
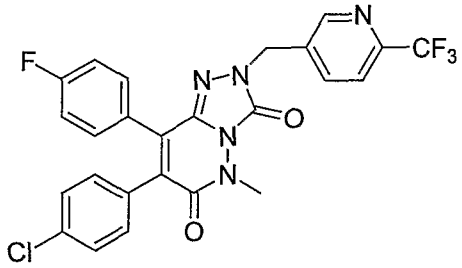
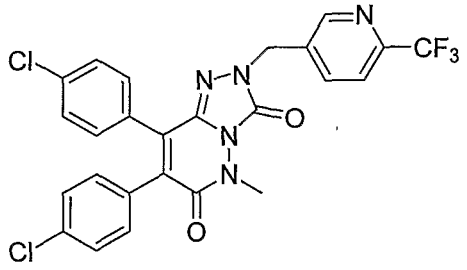
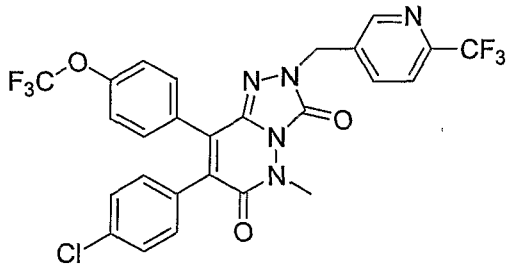
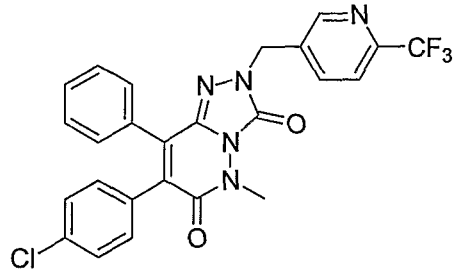
Set A:

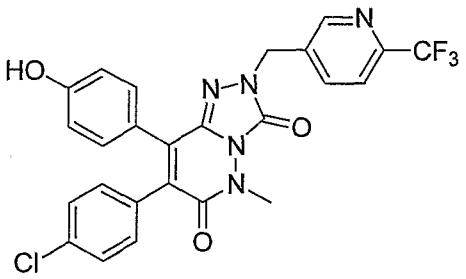
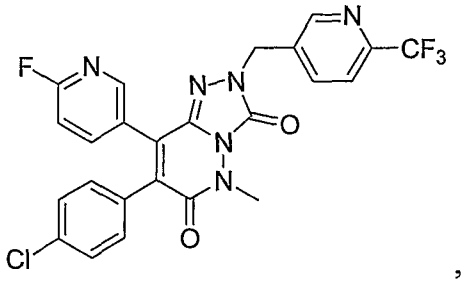
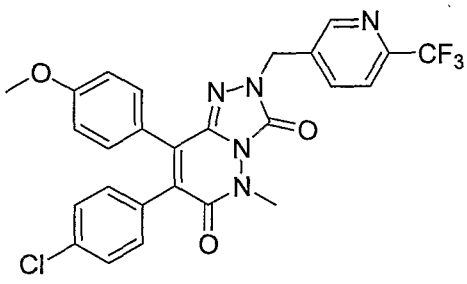
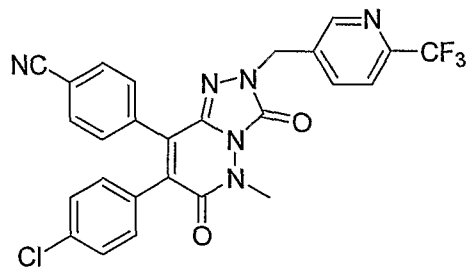
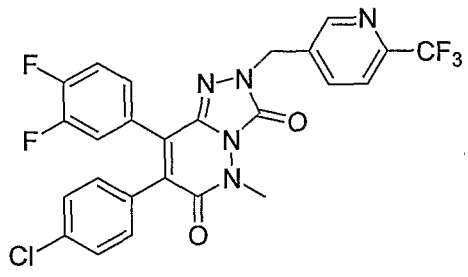
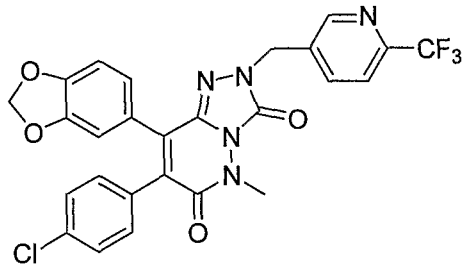

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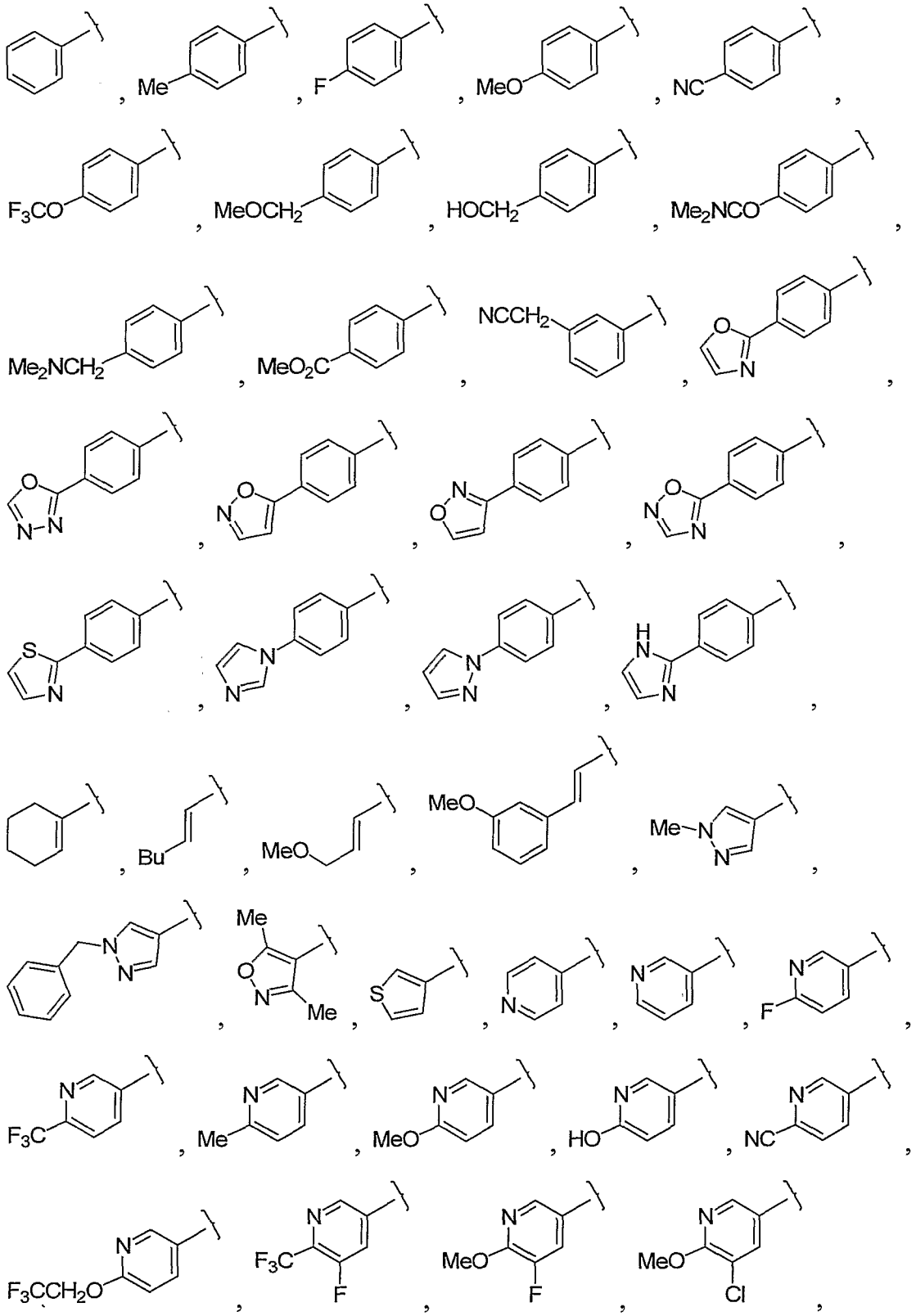

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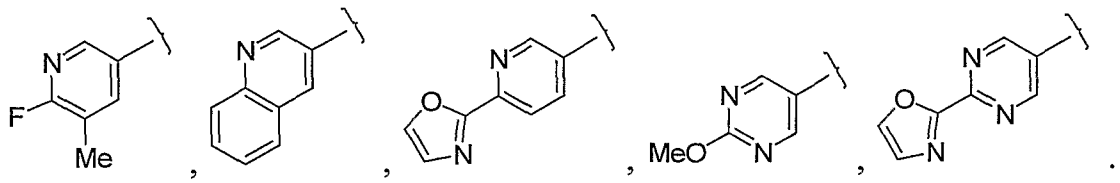

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As noted above, Set A consists of compounds that differ from one another only in the identity of R^1 with R^2 fixed as 4-chlorophenyl. Set A may be considered a one dimensional library of example compounds. Were one to vary both R^1 and R^2, a two 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.

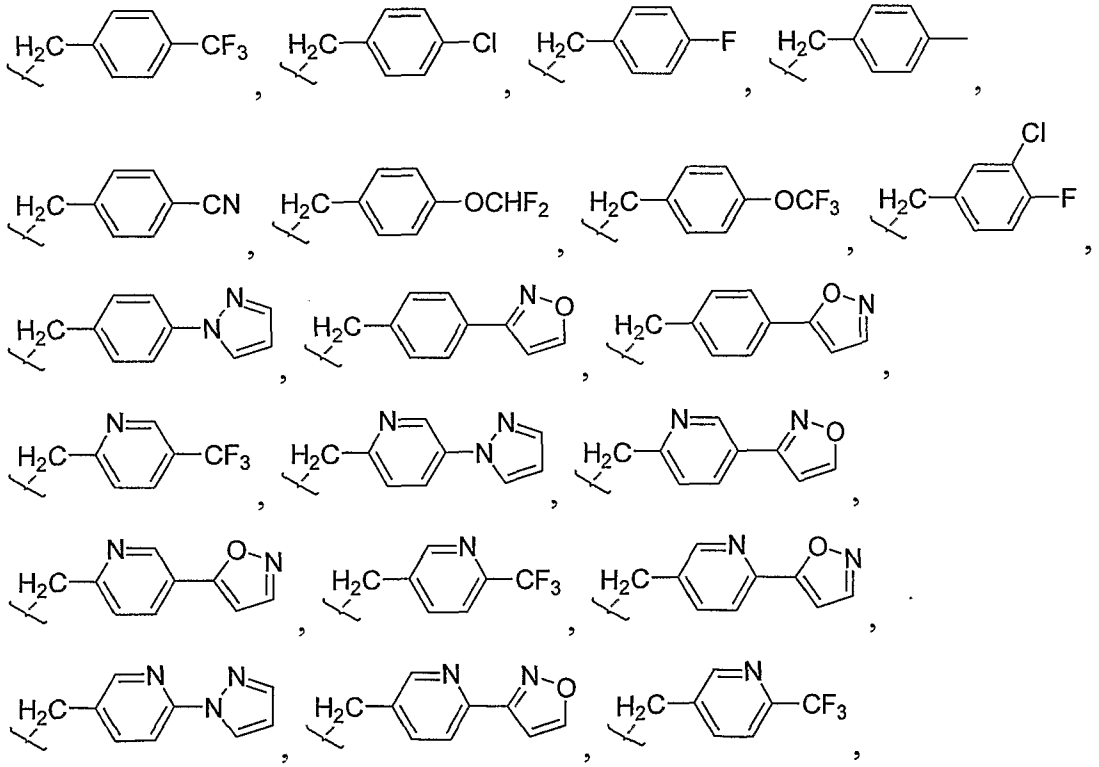
R^2 variants of Set B:

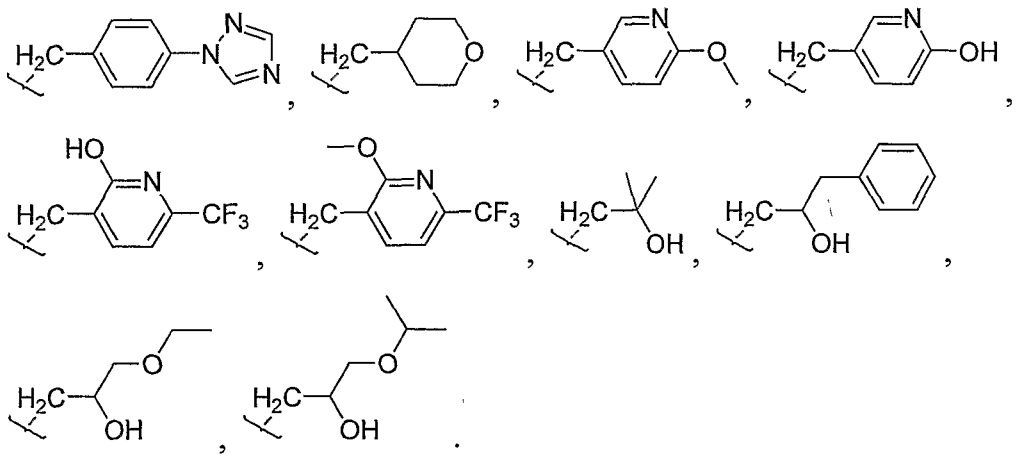




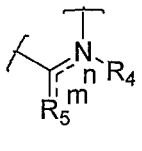
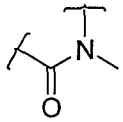
Further, as noted above, Set B is the two dimensional library that consists of all permutations of all of the variants of R^1 represented in Set A and a set of R^2 variants listed above with R^3 fixed as 2-(trifluoromethyl)pyridin-5-ylmethyl. Were one to vary R^1 and R^2 and R^3, a three dimensional 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:

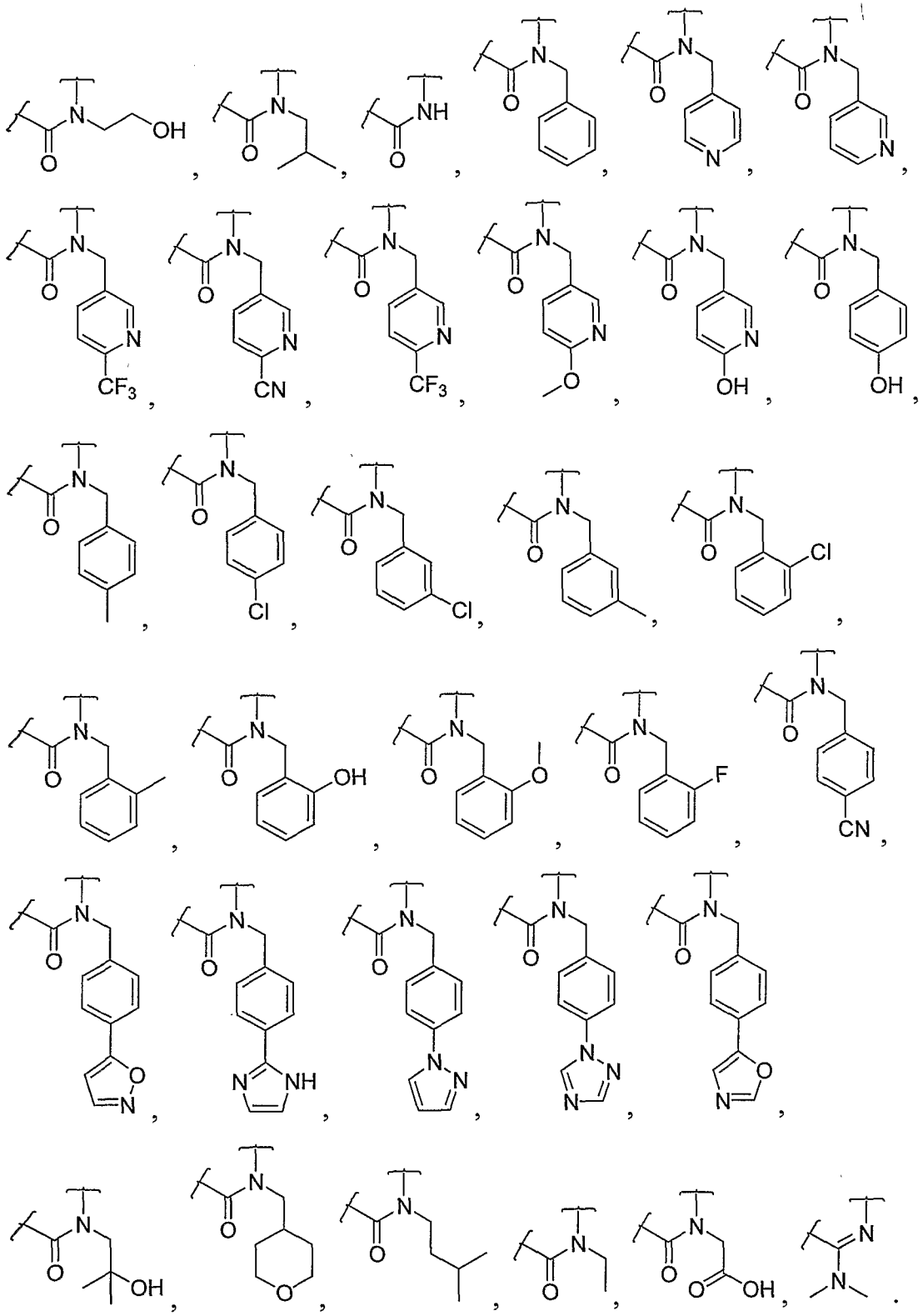




Further, as noted above, Set C is the three dimensional library that consists of all permutations of all of the variants of R^1 represented in Set A, all variants of R^2 represented in Set B, and variants listed above with R^4 fixed as methyl, R^5 is O, n is single bond and m is double bond. Were one to vary R^1 and R^2 and R^3, 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 R^1 represented in Set A, all of the R^2 variants listed above for Set B, all of the R^3 variants listed above for Set C and a set of R^4, R^5, 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.

R^4, R^5 n and m variants of Set D are depicted as , a fragment of formula I (for example, the depiction  represents a compound of formula I wherein R^4 is methyl, R^5 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 $CaCl_2$, 1 mM $MgCl_2$, 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 ^{3}H-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 K_i 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 uM 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-inducd 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/m^2) of at least 26. It may be due to any cause, whether genetic or environmental, including overeating and bulemia, polycycstic 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. Parkinsons's Disease is a neurodenerative 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 moeties 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 homograft (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 erythematosis); 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 hypopituatarism; Guillain-Barre syndrome; other autoimmune diseases; glomerulonephritis; serum sickness; uticaria; allergic diseases such as respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleracierma; mycosis fungoides; acute inflammatory and respiratory responses (such as acute respiratory distress syndrome and ishchemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplanteris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic schlerosis; 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 antagonsist, 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) inihibitors, 11-β-HSD-1 inhibitors, adinopectin 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-Welcome's GL-262570, englitazone (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.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller, et al., *J. Med. Chem.*, 31, 1869-1871 (1998) including isoprenoid (phosphinyl-methyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., *Current Pharmaceutical Design*, 2, 1-40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano, et al., *J. Med. Chem.*, 20, 243-249 (1977), the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, *J. Am. Chem. Soc.*, 98, 1291-1293 (1976), phosphinylphosphonates reported by McClard, R.W. et al., *J. Am. Chem. Soc.*, 109, 5544 (1987) and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

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, POLICEXIDE) and cholestagel (Sankyo/Geltex), as well as lipostabil (Rhone-

Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), 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(diallylmethylamine) 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 other hypolipidemic agent may be an ACAT inhibitor (which also has anti-atherosclerosis activity) such as disclosed in, *Drugs of the Future*, 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al., *Atherosclerosis* (Shannon, Irel), 137 (1), 77-85 (1998); "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, *Cardiovasc. Drug Rev.*, 16 (1), 16-30 (1998); "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al., *Bioorg. Med. Chem. Lett*, 6 (1), 47-50 (1996); "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al., Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., *Inflammation: Mediators Pathways*, 173-98 (1995), Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al., *Curr. Med. Chem.*, 1 (3), 204-25 (1994); "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)-methyl]ureas with enhanced hypocholesterolemic activity", Stout et al., *Chemtracts: Org. Chem.*, 8 (6), 359-62 (1995), or TS-962 (Taisho Pharmaceutical Co. Ltd), as well as F-1394, CS-505, F-12511, HL-004, K-10085 and YIC-C8-434.

The hypolipidemic agent may be an upregulator of LDL receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly). The

hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 (ezetimibe) as well as those disclosed in *Atherosclerosis* 115, 45-63 (1995) and *J. Med. Chem.* 41, 973 (1998).

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, glycitein or equol, or phytosterols, 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 1022272; a sodium-proton exchange inhibitor such as disclosed in DE 19622222; an LDL-receptor inducer 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 antihomocysteine 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 synthase 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, triamtrenene, 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.

Cannbinoid 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 (molindolone) 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, shcizoaffective 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, revastigraine, 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 transportor 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 azathiprine and cyclophosphamide, anticytokines such as antiIL-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 Medicine*, 337 (3), pp. 141-147 (1997).

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; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal 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).

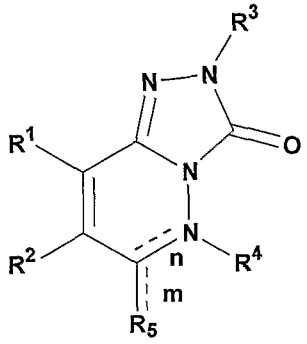
It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors

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.

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**,



I

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, $-NR^8R^9$, $-CO_2R^8$, $-CONR^8R^9$, $-OR^8$, $-NR^8COR^9$, $-NR^8CONR^8R^9$, $-NR^8CO_2R^9$, $-OCONR^8R^9$, $-NR^8S(O)_pR^9$, $-NR^8S(O)_pNR^8R^9$, $-NR^8S(O)_pOR^9$ and $-OS(O)_pNR^8R^9$;

R^2 is selected from the group consisting of halogen, cyano, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, $-NR^8R^9$, $-CO_2R^8$, $-CONR^8R^9$, $-OR^8$, $-NR^8COR^9$, $-NR^8CONR^8R^9$, $-NR^8CO_2R^9$, $-OCONR^8R^9$, $-NR^8S(O)_pR^9$, $-NR^8S(O)_pNR^8R^9$, $-NR^8S(O)_pOR^9$ and $-OS(O)_pNR^8R^9$;

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, $-OR^8$, $-NR^8R^9$, $-OCONR^8R^9$, $-NCR^8$, $-NCO_2R^8$ and $-NR^8S(O)_pR^9$ 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, heterocyclyl, 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, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$;

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

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

R^5 is O;

R^8 and R^9 are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, 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:

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

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

R^3 is selected from the group consisting of H, alkyl, cycloalkyl and heterocyclyl;

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

R^5 is O;

R^8 and R^9 are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, 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.

4. The compound according to Claim 3, wherein:

R^2 is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$.

5. The compound according to Claim 4, wherein:

R^1 is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$.

6. The compound according to Claim 5, wherein:

R^4 is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl.

7. The compound according to Claim 1, wherein:

R^1 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$;

R^2 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$;

R^3 is selected from the group consisting of H, alkyl, cycloalkyl and heterocyclyl;

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

R^5 is O;

R^8 and R^9 are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, 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.

8. The compound according to Claim 1, wherein:

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

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

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 selected from the group consisting of H, alkyl, cycloalkyl and heterocyclyl;

R^5 is O;

R^8 and R^9 are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, 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.

9. The compound according to Claim 8, wherein:

R^2 is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$.

10. The compound according to Claim 9, wherein:

R^1 is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$.

11. The compound according to Claim 10, wherein:

R^3 is selected from the group consisting of H, alkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl.

12. The compound according to Claim 1, wherein:

R^1 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$;

R^2 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$;

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

R^4 is selected from the group consisting of H and alkyl;

R^5 is O;

R^8 and R^9 are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, 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.

13. The compound according to Claim 1, wherein:

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

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

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;

R^5 is selected from the group consisting of halogen, $-OR^8$, $-NR^8R^9$, $-OCONR^8R^9$, $-NCR^8$, $-NCO_2R^8$, $-NR^8S(O)_pR^9$ when m is a single bond,

wherein the R^5 group has a molecular weight of less than 200 atomic mass units;

R^8 and R^9 are independently selected from H, alkyl, arylalkyl, cycloalkyl, heterocyclyl, 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 bond; and

n is a double bond.

14. The compound according to Claim 13, wherein:

R^2 is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$.

15. The compound according to Claim 14, wherein:

R^1 is selected from the group consisting of heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$.

16. The compound according to Claim 15, wherein:

R^3 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:

R^5 is selected from the group consisting of $-OR^8$ and $-NR^8R^9$;

wherein the R^5 group has a molecular weight of less than 200 atomic mass units;

18. The compound according to Claim 1, wherein:

R^1 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$;

R^2 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, $-OR^8$ and $-NR^8R^9$;

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

R^5 is selected from the group consisting of $-OR^8$, $-NR^8R^9$;

wherein the R^5 group has a molecular weight of less than 200 atomic mass units;

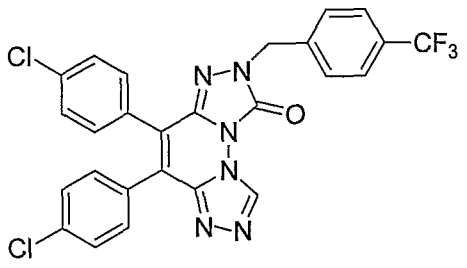
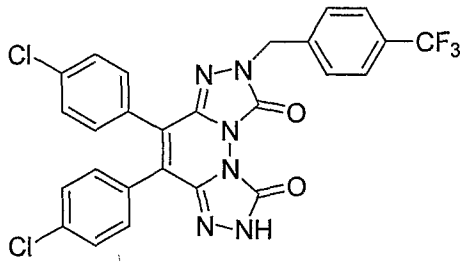
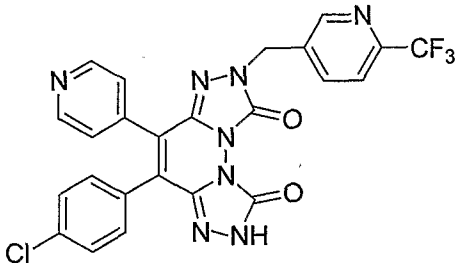
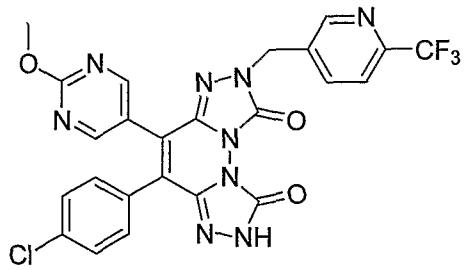
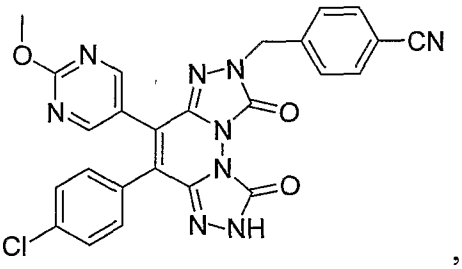
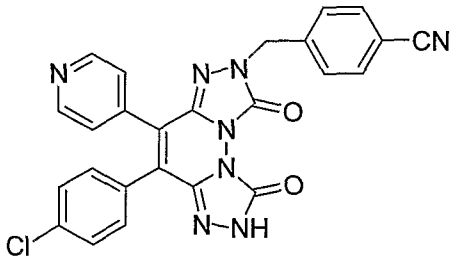
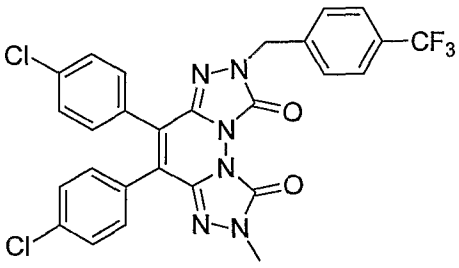
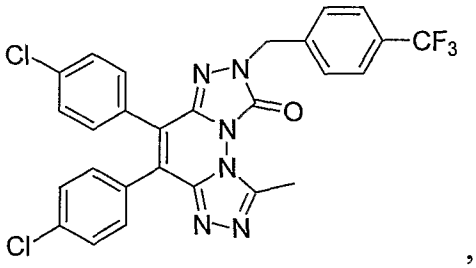
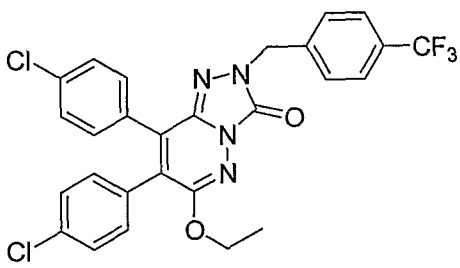
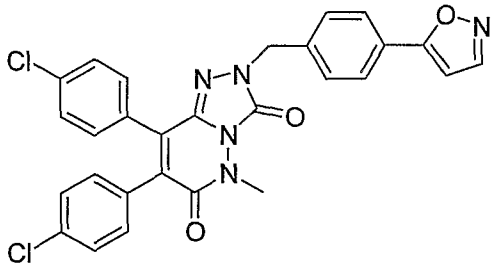
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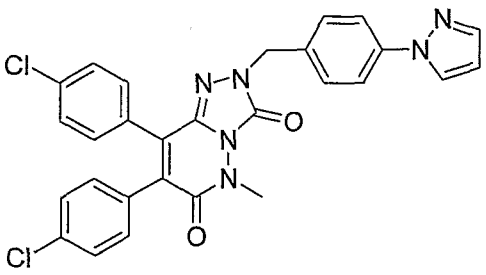
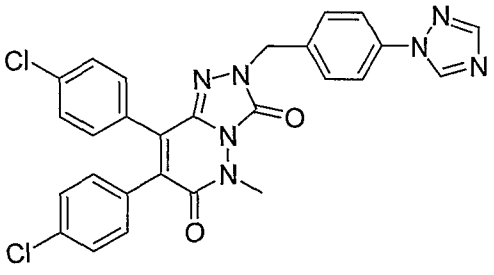
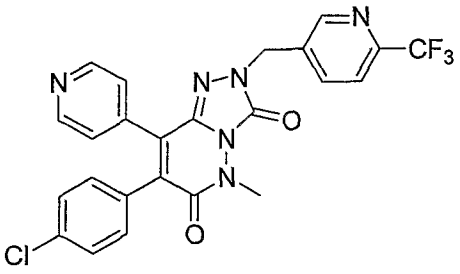
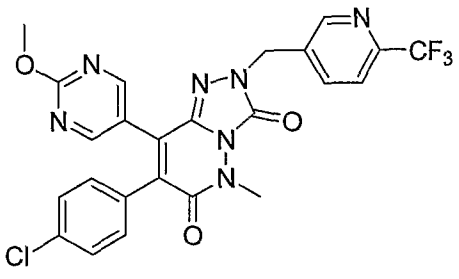
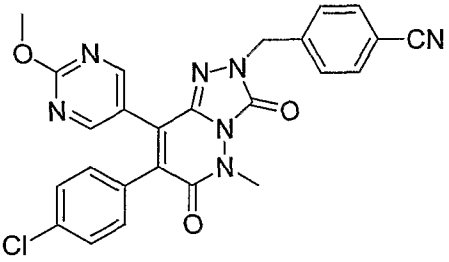
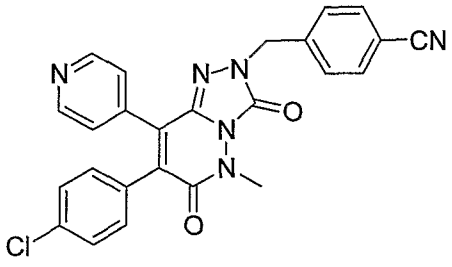
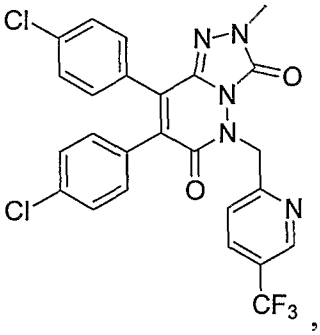
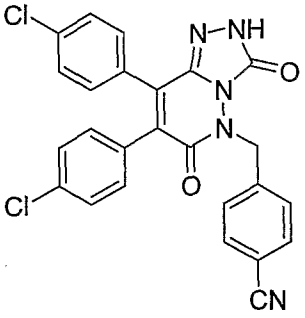
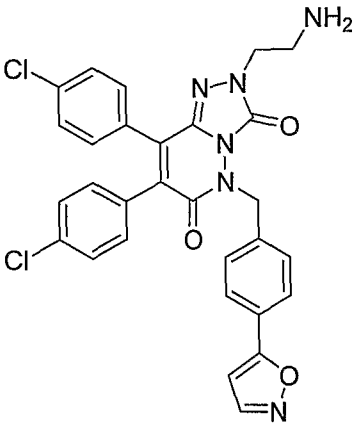
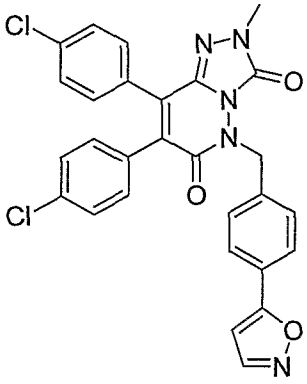
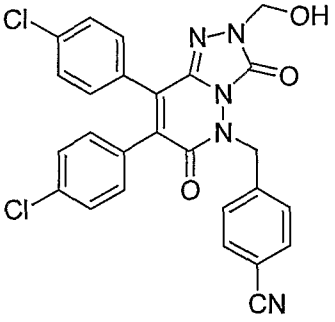
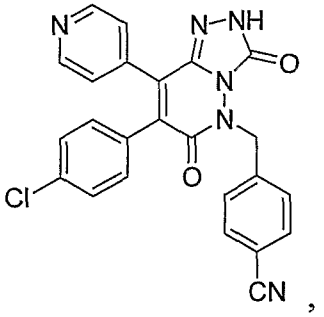
R^8 and R^9 can together form a 4, 5, 6, or 7 membered heterocyclyl ring or a 5 or 6 membered heteroaryl ring;

m is a single bond; and

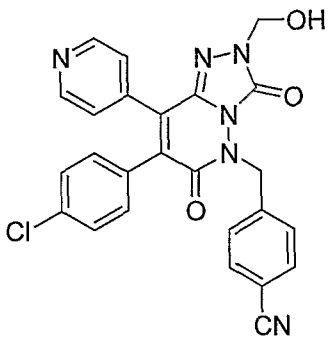
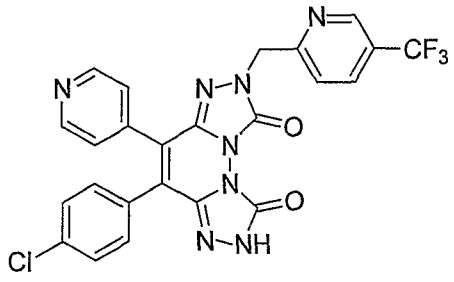
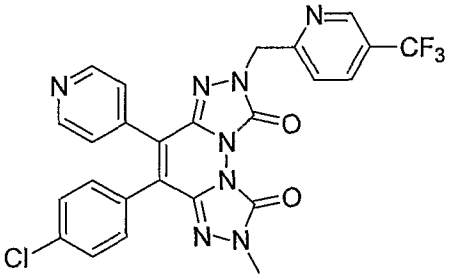
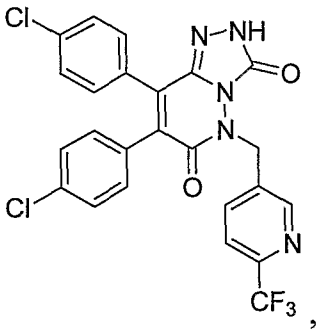
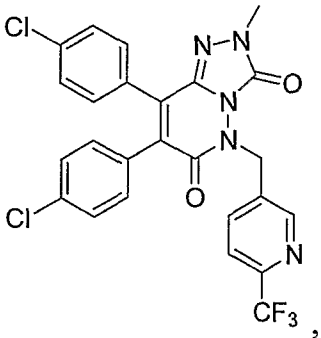
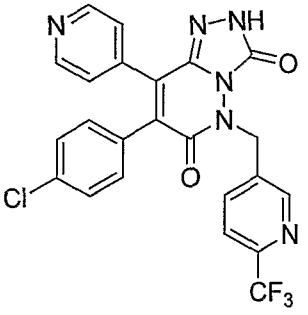
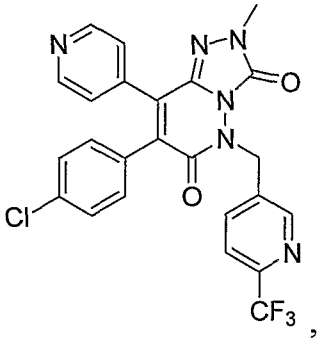
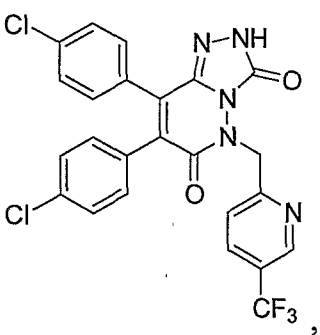
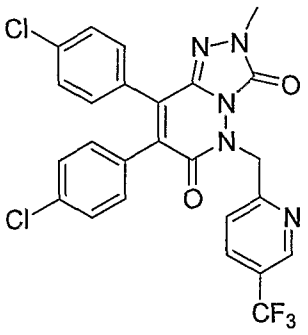
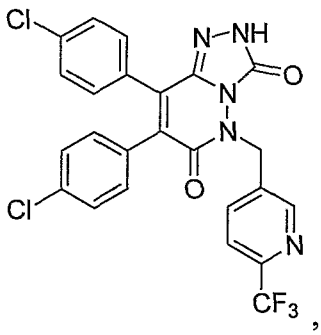
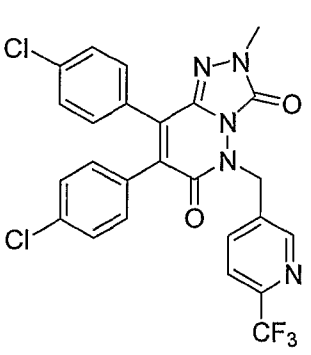
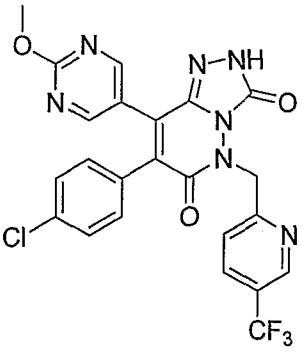
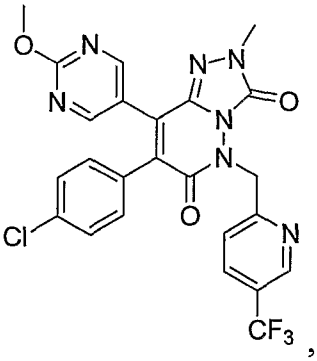
n is a double bond.

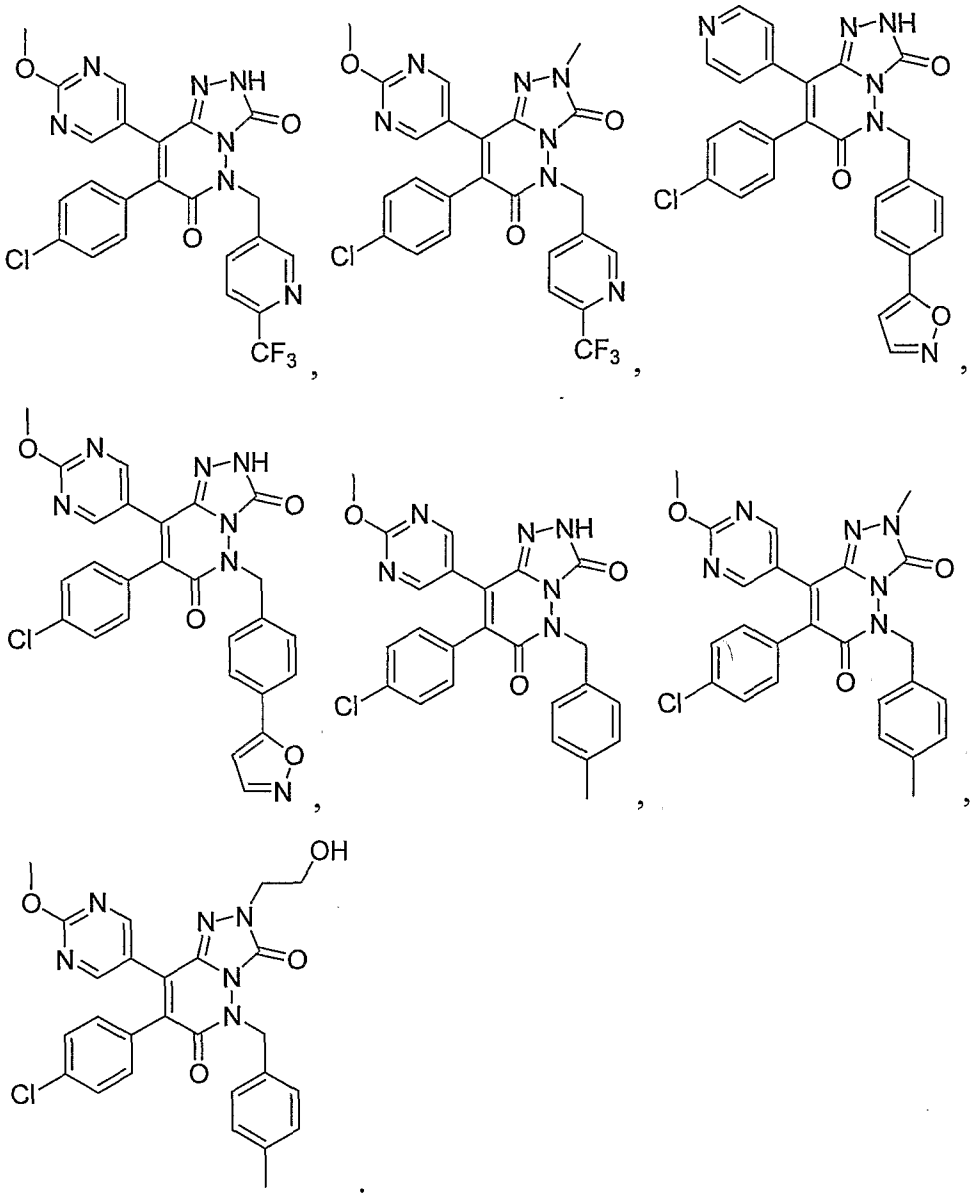
19. The compound of Claim 1 selected from:


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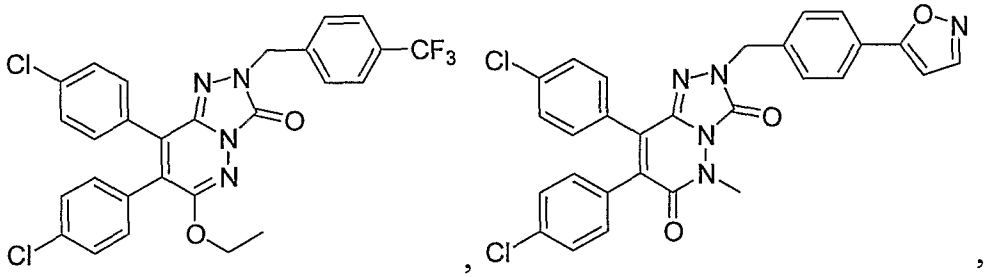

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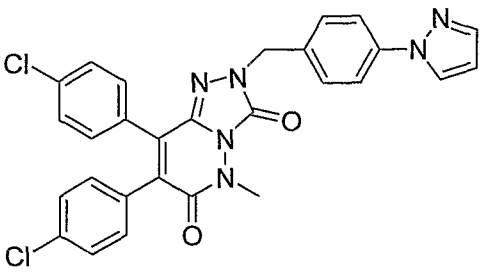
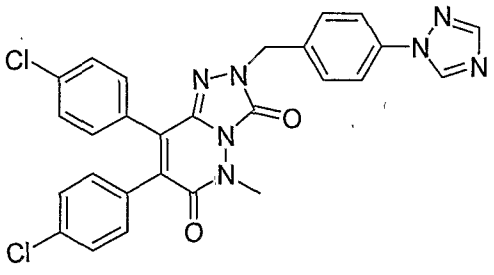
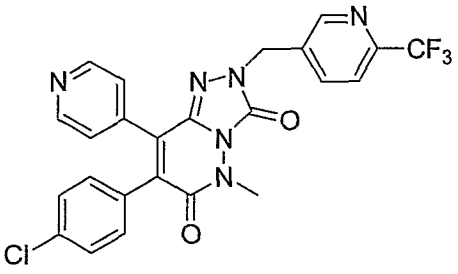
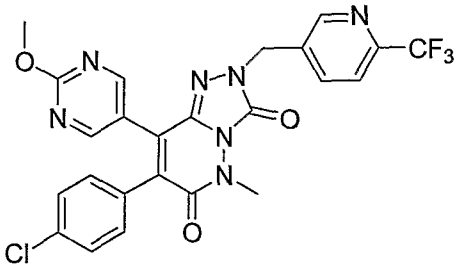
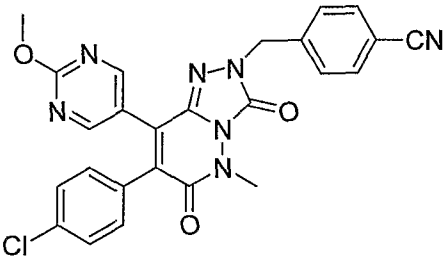
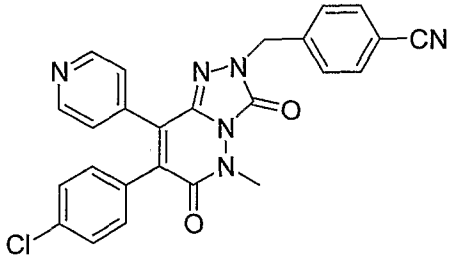
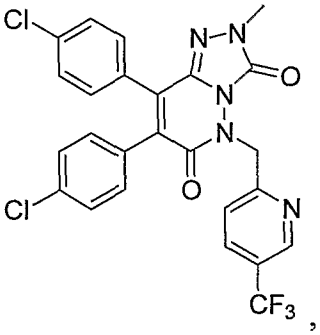
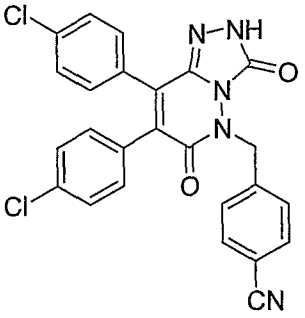
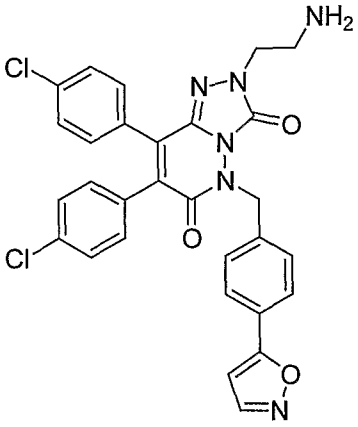
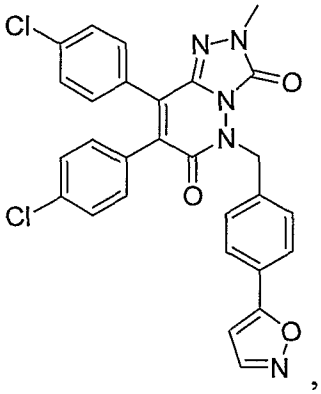
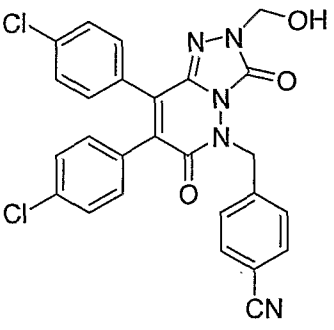
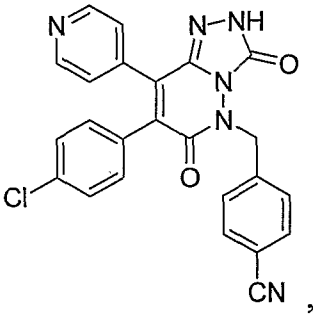
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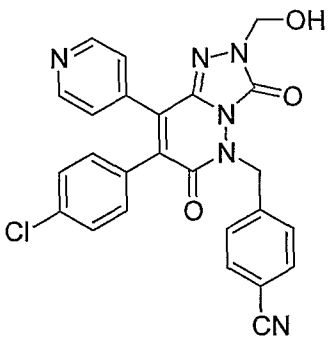
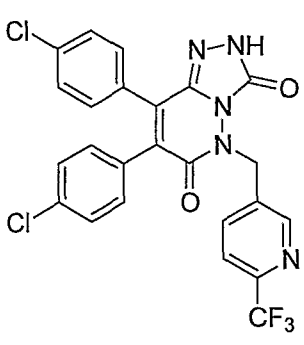
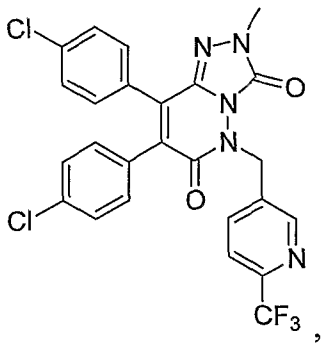
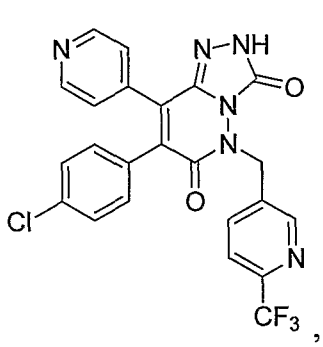
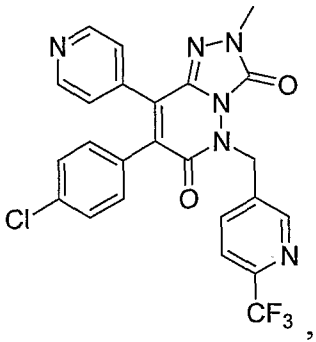
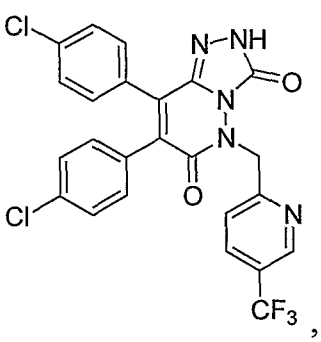
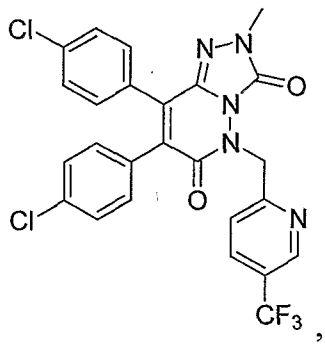
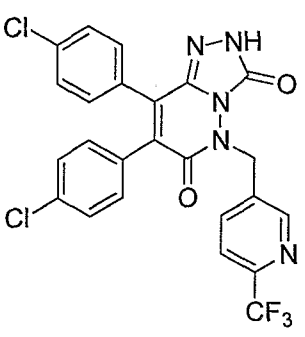
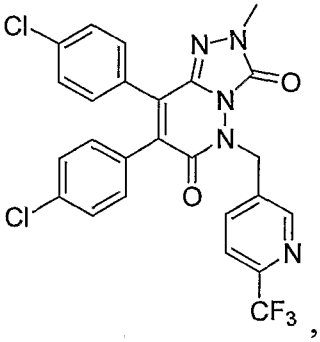
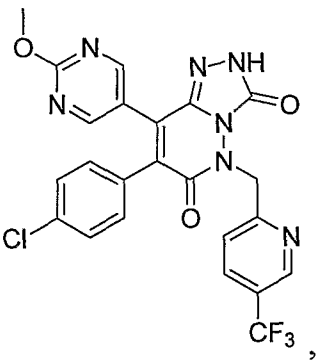
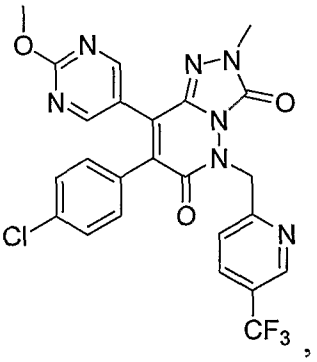
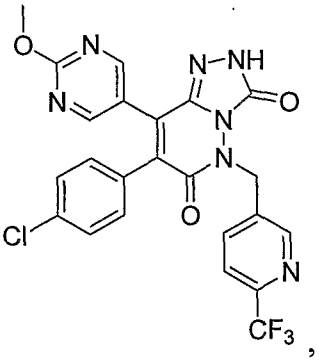

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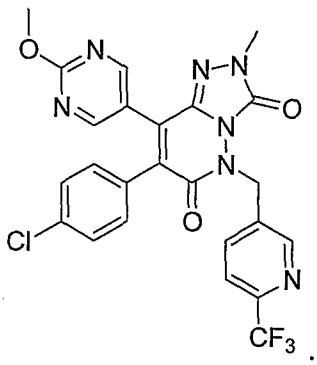


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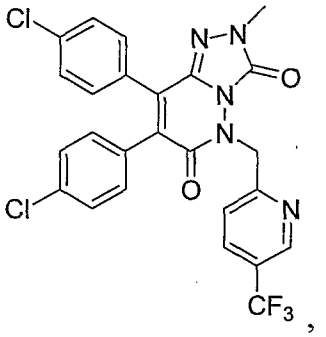
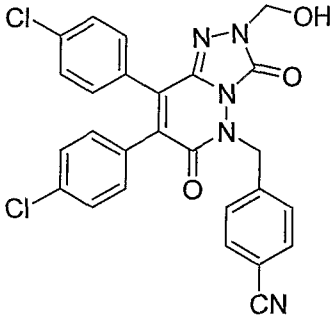
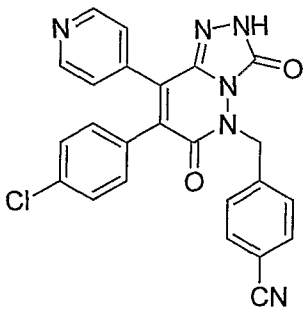
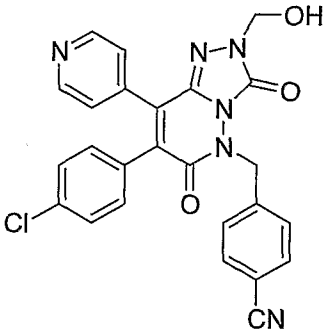
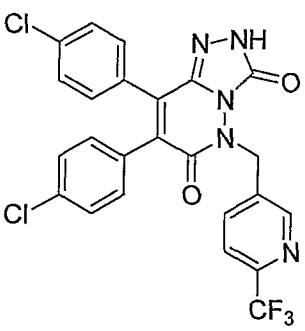
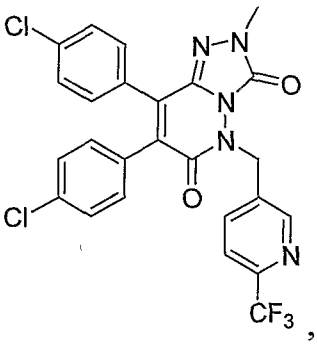
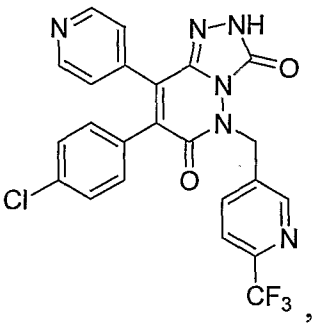
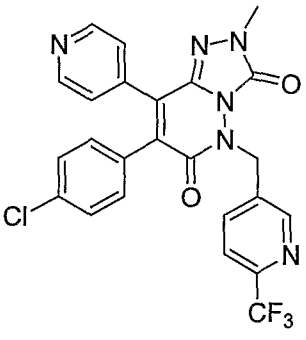
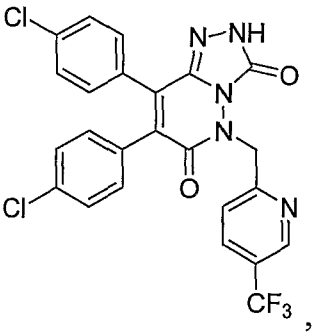


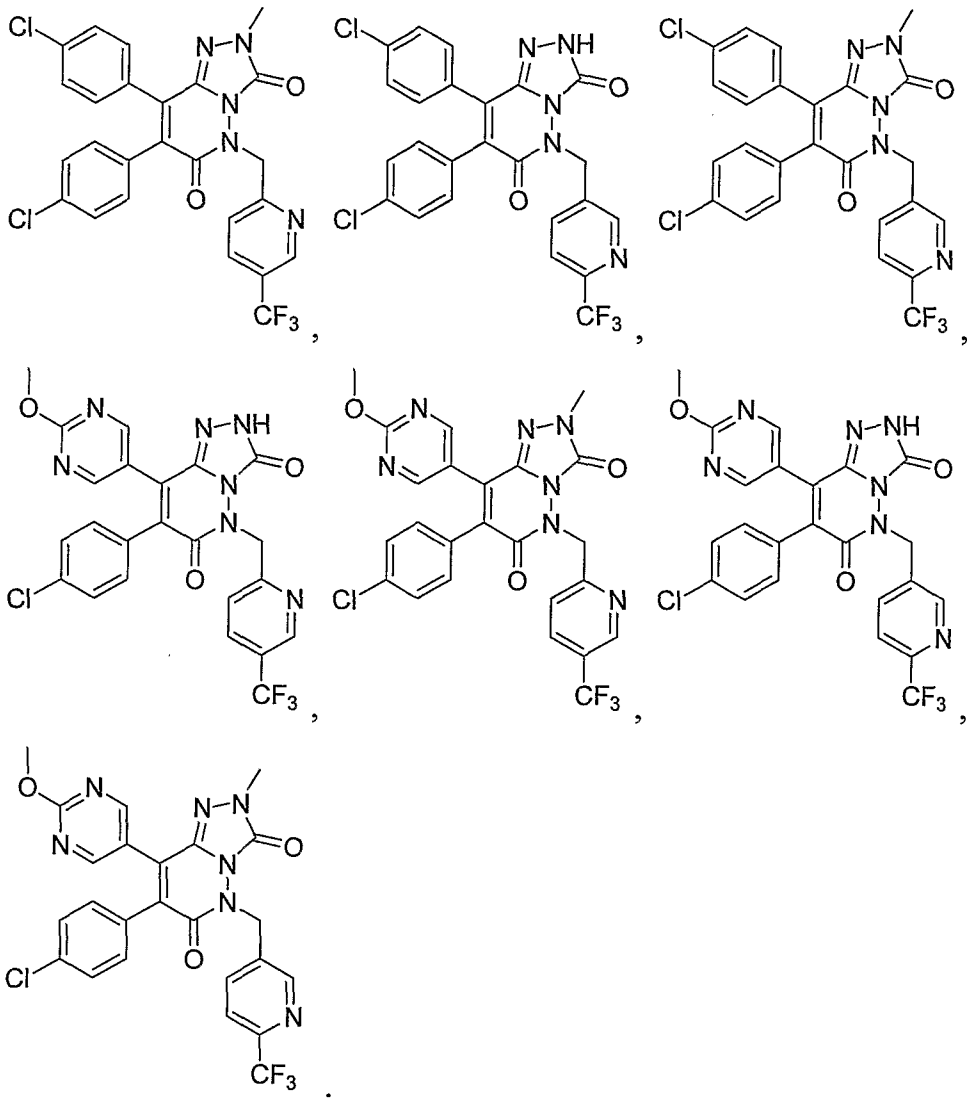

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21. The compound of Claim 1 selected from:


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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, gliclazide, 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-45355; 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; octahydronaphthalenes; 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 A 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; istigmastanylphosphorylcholine; 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-phenylcyclopentyl)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, glycitein or equol, or phytosterols, phytostanol and tocotrienol; a beta-lactam cholesterol absorption inhibitor; an HDL upregulator selected from an LXR agonist, a PPAR α-agonist and an FXR agonist; an LDL catabolism promoter; a sodium-proton exchange inhibitor; an LDL-receptor inducer; steroidal glycoside; an anti-oxidant selected from beta-carotene, ascorbic acid, α-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 δ 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, amlodipine and mybefradil; T-type calcium channel blockers selected from diltiazem, verapamil, nifedipine, amlodipine and mybefradil; diuretics selected from chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride and spironolactone; renin inhibitors; ACE inhibitors selected from captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril and lisinopril; AT-1 receptor antagonists selected from losartan, irbesartan and valsartan; ET receptor antagonists selected from sitaxsentan and atrsentan; Dual ET/AII antagonists; neutral endopeptidase inhibitors; vasopepsidase 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, olanzepine and aripiprazole; butyrophenone, including haloperidol; dipheyylbutylpiperidine, 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; revastigraine; 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 levadopa 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; eflunomide; 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; CD40Ig; 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; anticytokines selected from antiIL-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 appetitive 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 bulemia, polycycstic 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 erythematosis; 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 hypopituatarism; Guillain-Barre syndrome; other autoimmune diseases; glomerulonephritis; serum sickness; uticaria; asthma, hayfever, allergic rhinitis and skin allergies; scleracierma; mycosis fungoides; acute inflammatory and respiratory responses, including acute respiratory distress syndrome and ishchemia/reperfusion injury; dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema; Behcet's disease; Pustulosis palmoplanteris; Pyoderma gangrenum; Sezary's syndrome; atopic dermatitis; systemic schlerosis; 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.