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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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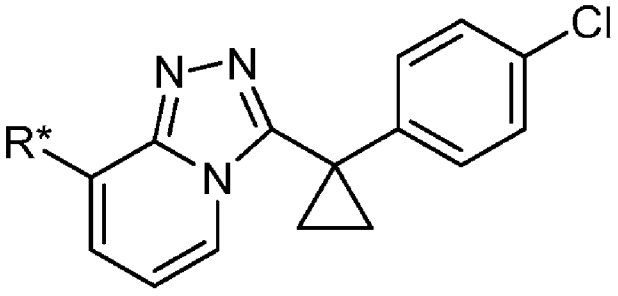
[Continued on next page]

(54) Title: ISOTOPICALLY LABELED TRIAZOLOPYRIDINE 11-BETA HYDROXYSTEROID DEHYDROGENASE TYPE I INHIBITORS



I

(57) Abstract: Novel compounds are provided which are 11-beta-hydroxysteroid dehydrogenase type I inhibitors. 11-beta-hydroxysteroid dehydrogenase type I inhibitors are useful in treating, preventing, or slowing the progression of diseases requiring 11-beta-hydroxysteroid dehydrogenase type I inhibitor therapy. These novel compounds of formula I: or stereoisomers or pharmaceutically acceptable salts thereof, wherein R* is an isotopically labeled hydroxypropyl moiety.

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ISOTOPICALLY LABELED TRIAZOLOPYRIDINE 11-BETA HYDROXYSTEROID DEHYDROGENASE TYPE I INHIBITORS

CROSS-REFERENCES TO RELATED APPLICATION

This application claims priority benefit under Title 35 § 119(e) of United States provisional Application 61/893,991 filed October 22, 2013, the contents of which are herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

The steroid hormone cortisol is a key regulator of many physiological processes. However, an excess of cortisol, as occurs in Cushing's Disease, provokes severe metabolic abnormalities including: type 2 diabetes, cardiovascular disease, obesity, and osteoporosis. Many patients with these diseases, however, do not show significant increases in plasma cortisol levels. In addition to plasma cortisol, individual tissues can regulate their glucocorticoid tone via the in situ conversion of inactive cortisone to the active hormone cortisol. Indeed, the normally high plasma concentration of cortisone provides a ready supply of precursor for conversion to cortisol via the intracellular enzyme 11-beta-hydroxysteroid dehydrogenase type I (11beta-HSD1).

11beta-HSD1 is a member of the short chain dehydrogenase superfamily of enzymes. By catalyzing the conversion of cortisone to cortisol, 11beta-HSD1 controls the intracellular glucocorticoid tone according to its expression and activity levels. In this manner, 11beta-HSD1 can determine the overall metabolic status of the organ. 11beta-HSD1 is expressed at high levels in the liver and at lower levels in many metabolically active tissues including the adipose, the CNS, the pancreas, and the pituitary. Taking the example of the liver, it is predicted that high levels of 11beta-HSD1 activity will stimulate gluconeogenesis and overall glucose output. Conversely, reduction of 11beta-HSD1 activity will down regulate gluconeogenesis resulting in lower plasma glucose levels.

Various studies have been conducted that support this hypothesis. For example, transgenic mice expressing 2X the normal level of 11beta-HSD1 in only the adipose tissue show abdominal obesity, hyperglycemia, and insulin resistance.

(Masuzaki, H. et al., "A Transgenic Model of Visceral Obesity and the Metabolic Syndrome", *Science*, 294:2166-2170 (2001). Conversely, when the 11beta-HSD1 gene is ablated by homologous recombination, the resulting mice are resistant to diet induced obesity and the accompanying dysregulation of glucose metabolism (Morton, N.M. et al., "Novel Adipose Tissue-Mediated Resistance to Diet-induced Visceral Obesity in 11β-Hydroxysteroid Dehydrogenase Type 1-Deficient Mice", *Diabetes*, 53:931-938 (2004). In addition, treatment of genetic mouse models of obesity and diabetes (ob/ob, db/db and KKAy mice) with a specific inhibitor of 11beta-HSD1 causes a decrease in glucose output from the liver and an overall increase in insulin sensitivity (Alberts, P. et al., "Selective Inhibition of 11β-Hydroxysteroid Dehydrogenase Type I Improves Hepatic Insuling Sensitivity in Hyperglycemic Mice Strains", *Endocrinology*, 144:4755-4762 (2003)). Furthermore, inhibitors of 11beta-HSD1 have been shown to be effective in treating metabolic syndrome and atherosclerosis in high fat fed mice (Hermanowski-Vosatka et al., *J. Exp. Med.*, 202(4):517-527 (2002)). Based in part on these studies, it is believed that local control of cortisol levels is important in metabolic diseases in these model systems. In addition, the results of these studies also suggest that inhibition of 11beta-HSD1 will be a viable strategy for treating metabolic diseases such as type 2 diabetes, obesity, and the metabolic syndrome.

Lending further support to this idea are the results of a series of preliminary clinical studies. For example, several reports have shown that adipose tissue from obese individuals has elevated levels of 11beta-HSD1 activity. In addition, studies with carbenoxolone, a natural product derived from licorice that inhibits both 11beta-HSD1 and 11beta-HSD2 (converts cortisol to cortisone in kidney) have shown promising results. A seven day, double blind, placebo controlled, cross over study with carbenoxolone in mildly overweight individuals with type 2 diabetes showed that patients treated with the inhibitor, but not the placebo group, displayed a decrease in hepatic glucose production (Andrews, R.C. et al., *J. Clin. Endocrinol. Metab.*, 88:285-291 (2003)). This observation is consistent with the inhibition of 11beta-HSD1 in the liver. The results of these preclinical and early clinical studies strongly support the concept that treatment with a potent and selective inhibitor of 11beta-

HSD1 will be an efficacious therapy in patients afflicted with type 2 diabetes, obesity, and the metabolic syndrome.

Accordingly, compounds that activate 11beta-HSD1 could demonstrate a wide range of utilities in treating diabetes and related conditions, microvascular complications associated with diabetes, the macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, inflammatory diseases and other maladies. PCT Publication Nos. WO 2006/135667 A1, WO 2006/135795 A1, WO 2008/024892 A1, WO 2008/130951 A1, WO 2009/045753 A1 (incorporated herein by reference and assigned to present applicant) and WO 2009/102761 A1, disclose compounds that activate 11beta-HSD1. The references also disclose various processes to prepare these compounds.

It is desirable to find new compounds with improved pharmacological characteristics compared with known 11beta-HSD1 activators. For example, it is desirable to find new compounds with improved 11beta-HSD1 activity and selectivity for 11beta-HSD1 versus other dehydrogenase receptors (*i.e.*, 11beta-HSD2 receptor). It is also desirable to find compounds with advantageous and improved characteristics in one or more of the following categories:

(a) pharmaceutical properties (*i.e.*, solubility, permeability, amenability to sustained release formulations);

(b) dosage requirements (*e.g.*, lower dosages and/or once-daily dosing);

(c) factors which decrease blood concentration peak-to-trough characteristics (*i.e.*, clearance and/or volume of distribution);

(d) factors that increase the concentration of active drug at the receptor (*i.e.*, protein binding, volume of distribution);

(e) factors that decrease the liability for clinical drug-drug interactions (cytochrome P450 enzyme inhibition or induction, such as CYP 2D6 inhibition, see Dresser, G.K. et al., *Clin. Pharmacokinet.*, 38:41-57 (2000), which is hereby incorporated by reference); and

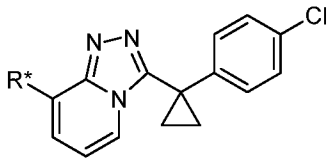
(f) factors that decrease the potential for adverse side-effects (*e.g.*, pharmacological selectivity beyond the intracellular enzyme 11-beta-hydroxysteroid dehydrogenase type I, potential chemical or metabolic reactivity, limited CNS penetration, ion-channel selectivity). It is especially desirable to find compounds

having a desirable combination of the aforementioned pharmacological characteristics.

SUMMARY OF THE INVENTION

The present invention relates to isotopically-labeled compounds, wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon such as ^{11}C, ^{13}C, and ^{14}C, chlorine, such as ^{36}Cl, fluorine such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O, and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S.

In accordance with the present invention, bicyclic and related compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, are provided that have the general structure of formula I:



I

wherein R* is an isotopically labeled hydroxypropyl moiety.

The compounds of the present invention are believed to inhibit the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I. Consequently, the compounds of the present invention may be used in the treatment of multiple diseases or disorders associated with 11-beta-hydroxysteroid dehydrogenase type I, such as diabetes and related conditions, microvascular complications associated with diabetes, the macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, inflammatory diseases and other maladies. Examples of diseases or disorders associated with the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I that can be prevented, inhibited, or treated according to the present invention include, but are not limited to,

diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae (acute coronary syndrome, myocardial infarction, angina pectoris, peripheral vascular disease, intermittent claudication), abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy, glaucoma and inflammatory diseases, such as, rheumatoid arthritis, Cushing's Disease, Alzheimer's Disease and osteoarthritis.

The present invention provides for compounds of formula I or II, pharmaceutical compositions employing such compounds, and for methods of using such compounds. In particular, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I or II alone or in combination with a pharmaceutically acceptable carrier.

Further, in accordance with the present invention, a method is provided for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I, such as defined above and hereinafter, wherein a therapeutically effective amount of a compound of formula I or II is administered to a mammalian, i.e., human, patient in need of treatment.

The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

Further, the present invention provides a method for preventing, inhibiting, or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of formula I or II and another compound of formula I or II and/or at least one other type of therapeutic agent, is administered to a mammalian, i.e., human, patient in need of treatment.

The present invention also describes compounds that are believed to have a beneficial improvement in metabolic stability, in particular, metabolic stability in

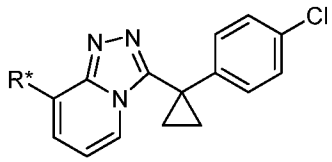
human liver microsomes, in comparison to compounds previously disclosed in the art, such as those disclosed in PCT Publication No. WO 2009/045753 A1.

Additionally, compounds of the present invention are believed to have a beneficial, preferably a two-fold, more preferably, a three-fold, decrease in liability for clinical drug-drug interactions (cytochrome P450 enzyme inhibition or induction, such as CYP 2C19 inhibition) in comparison to compounds previously disclosed in the art, such as those disclosed in PCT Publication No. WO 2009/045753 A1.

Furthermore, compounds of the present invention are believed to show unexpected advantages over compounds previously disclosed in the art, such as those disclosed in PCT Publication No. WO 2009/045753 A1. The present compounds are believed to have a desirable combination of decreased liability for clinical drug-drug interactions (cytochrome P450 enzyme inhibition or induction, such as CYP 2C19 inhibition) and metabolic stability in a human liver microsomal assay without a loss in pharmacological activity. Such compounds should be more useful in the treatment, inhibition or amelioration of one or more diseases or disorders that are discussed herein.

DESCRIPTION OF THE INVENTION

In accordance with the present invention, compounds of formula I



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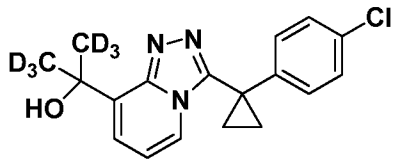
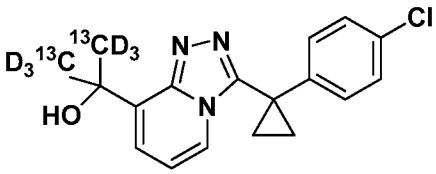
or enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof wherein wherein R* is an isotopically labeled hydroxypropyl moiety.

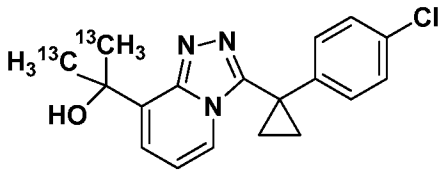
In yet another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of formula Ia, Ib, Ic, Id, Ie, If or Ig:



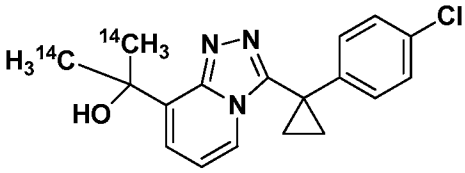
Ia ;



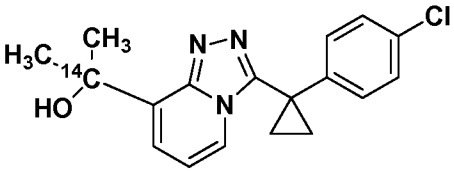
Ib ;



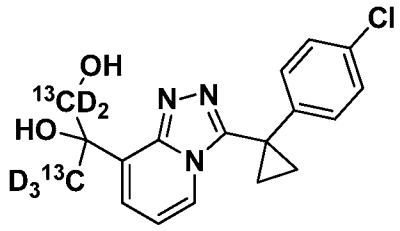
Ic ;



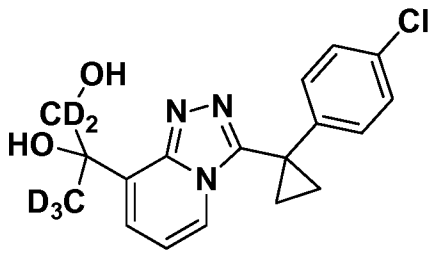
Id ;



Ie ;



If ; or



Ig.

In another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula Ia or Ib.

In another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula Ia.

In another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula Ib.

In another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula Ic.

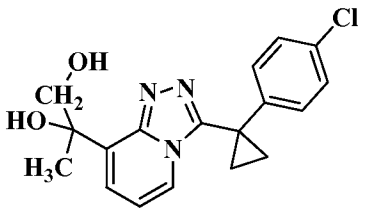
In another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula Id.

In another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula Ie.

In another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula If.

In another embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula Ig.

In one embodiment, the present invention provides compounds, enantiomers, diastereomers, tautomers, prodrugs, solvates or salts thereof, wherein the compounds are compounds of Formula II:



II.

In another embodiment, the present invention relates to pharmaceutical compositions comprised of a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone or, optionally, in combination with a pharmaceutically acceptable carrier and/or one or more other agent(s).

In another embodiment, the present invention relates to methods of inhibiting the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I comprising administering to a mammalian patient, for example, a human patient, in need thereof a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or optionally, in combination with another compound of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diseases or disorders associated with the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

Examples of diseases or disorders associated with the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I that can be prevented, inhibited, or treated according to the present invention include, but are not limited to, diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia,

retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis, acute coronary syndrome, myocardial infarction, angina pectoris, peripheral vascular disease, intermittent claudication, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis, pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy, glaucoma, rheumatoid arthritis, Cushing's Disease, Alzheimer's Disease and osteoarthritis.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diabetes, hyperglycemia, obesity, dyslipidemia, hypertension, cognitive impairment, rheumatoid arthritis, osteoarthritis, glaucoma, Cushing's Disease and Metabolic Syndrome comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In still another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of diabetes, comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In yet still another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of hyperglycemia comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of obesity comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In one embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of dyslipidemia comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of hypertension comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of cognitive impairment comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of rheumatoid arthritis comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a

compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of osteoarthritis comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of Metabolic Syndrome comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of glaucoma comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

In another embodiment, the present invention relates to a method for preventing, inhibiting, or treating the progression or onset of Cushing's Disease comprising administering to a mammalian patient, for example, a human patient, in need of prevention, inhibition, or treatment a therapeutically effective amount of a compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone, or, optionally, in combination with another compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II and/or at least one other type of therapeutic agent.

The invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention also encompasses all combinations of alternative aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment to describe additional embodiments of the present invention. Furthermore, any elements of an embodiment may be combined with any and all other elements from any of the embodiments to describe additional embodiments.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

One enantiomer of a compound of the present invention may display superior activity compared with the other. Thus, all of the stereochemistries are considered to be a part of the present invention. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Young, S.D. et al., *Antimicrobial Agents and Chemotherapy*, 2602-2605 (1995).

To the extent that compounds of the present invention, and salts thereof, may exist in their tautomeric form, all such tautomeric forms are contemplated herein as part of the present invention.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, bisulfate and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985), the disclosure of which is hereby incorporated by reference.

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

The term "prodrugs" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of the present invention 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.

Various forms of prodrugs are well known in the art and are described in:

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

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

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

d) *Hydrolysis in Drug and Prodrug Metabolism*, Bernard Testa and Joachim M. Mayer (Wiley-VCH, 2003).

Said references are incorporated herein by reference.

In addition, compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% formula I or II compound ("substantially pure" compound I or II), which is then used or formulated as described herein. Such "substantially pure" compounds of the formula I or II are also contemplated herein as part of the present invention.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms and/or exhibit polymorphism. Consequently, compounds of the present invention 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 or fractional crystallization. In addition, the compounds of present invention may exist in tautomeric form. Such

tautomeric forms of the formula I or II are also contemplated herein as part of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation, handling and storage to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to inhibit the activity of the enzyme 11-beta-hydroxysteroid dehydrogenase type I or effective to treat or prevent metabolic or other disorders.

As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, i.e., arresting it development; and/or (c) relieving the disease-state, i.e., causing regression of the disease state.

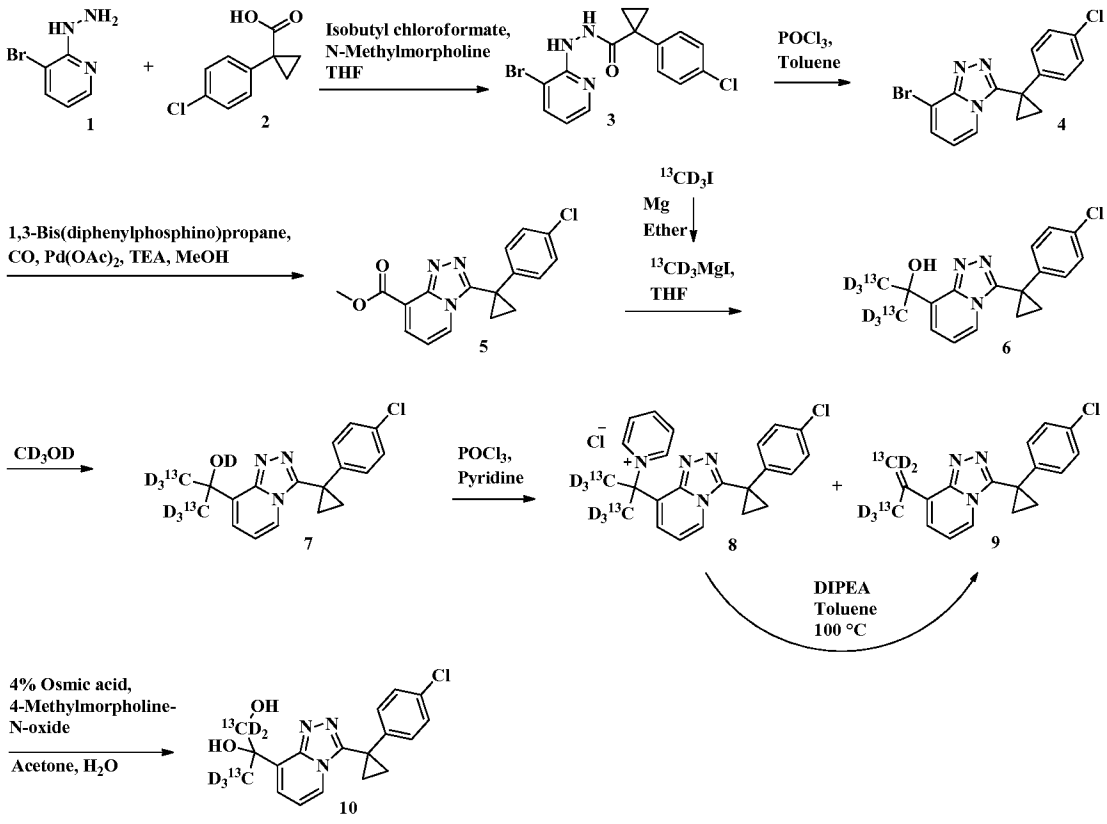
SYNTHESIS

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereof as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety by reference.

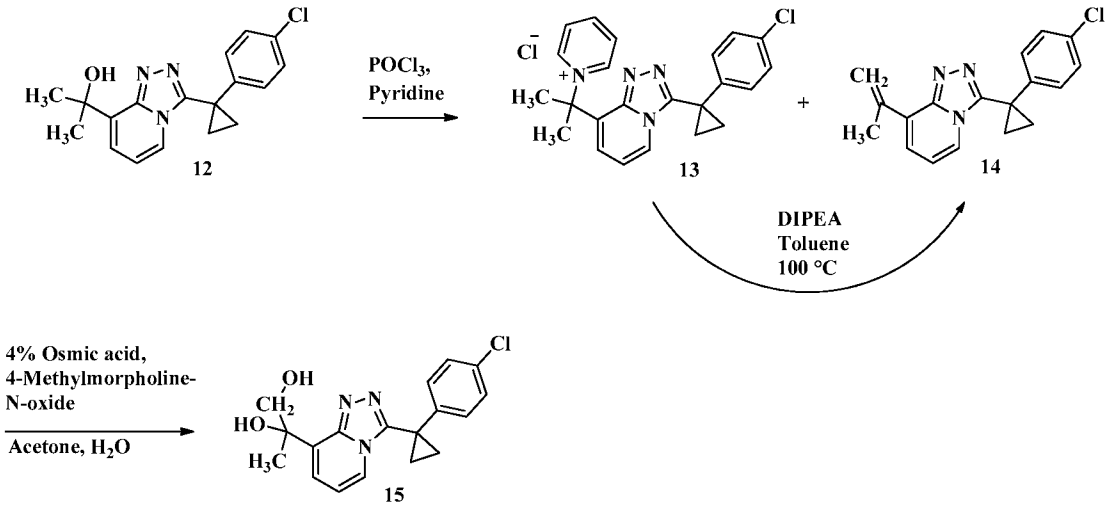
The novel compounds of Formula I may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being affected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including

solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. One skilled in the art of organic synthesis understands that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Not all compounds of Formula I falling into a given class may be compatible with some of the reaction conditions required in some of the methods described. Such restrictions to the substituents, which are compatible with the reaction conditions, will be readily apparent to one skilled in the art and alternate methods must be used.

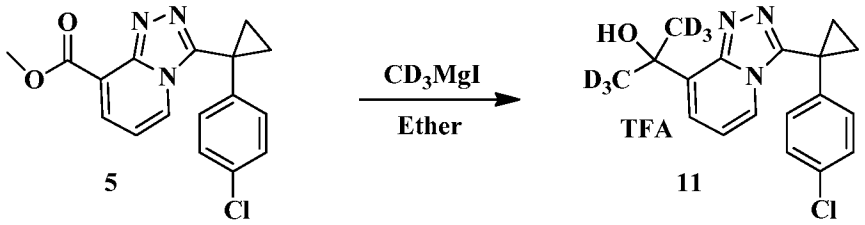
Scheme 1



Scheme 2


Cl
OH
N-N
H3C
H3C
12
POCl3,
Pyridine
Cl
Cl
+N
H3C
H3C
13
+
CH2
H3C
14
DIPEA
Toluene
100 °C
4% Osmic acid,
4-Methylmorpholine-
N-oxide
Acetone, H2O
OH
CH2
HO
H3C
15

Scheme 3



EXAMPLES

The following Examples are offered as illustrative as a partial scope and particular embodiments of the invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the compounds described herein have been prepared, isolated and characterized using the Schemes and other methods disclosed herein or may be prepared using the same.

As appropriate, reactions were conducted under an atmosphere of dry nitrogen (or argon). For anhydrous reactions, DRISOLV® solvents from EM or anhydrous solvents from Sigma-Aldrich were employed. For other reactions, reagent grade or HPLC grade solvents were utilized. Unless otherwise stated, all commercially obtained reagents were used as received.

LC/MS measurements were obtained using a Shimadzu HPLC/Waters ZQ single quadrupole mass spectrometer hybrid system or a Finnigan LXQ LC/MS System. Data for the peak of interest are reported from positive-mode electrospray ionization. NMR (nuclear magnetic resonance) spectra were typically obtained on Bruker or JEOL 300 MHz, 400 MHz and 500 MHz instruments in the indicated solvents. All chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. ^{1}H-NMR spectral data are typically reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, sep = septet, m = multiplet, app = apparent), coupling constants (Hz), and integration.

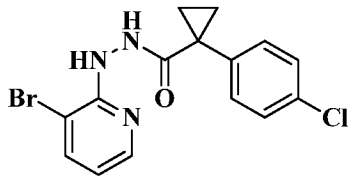
One of skill in the art will recognize the standard abbreviations utilized herein, throughout the specification. For ease of reference, the abbreviations include, but are not necessarily limited to: sat. = saturated, HPLC = high-performance liquid

chromatography, AP = area percent, KF = Karl-Fischer, RT = room temperature, mmol = millimoles, MS = mass spectroscopy, $CDCl_3$ = deuterated chloroform, CD_3OD = deuterated methanol, NMP = N-methylpyrrolidone, TEA = triethylamine, DIPEA = Diisopropylethylamine, IPA = isopropyl alcohol, TFA = trifluoroacetic acid, HCl = hydrochloric acid, EtOAc = ethyl acetate, CH_2Cl_2 = methylene chloride, THF = tetrahydrofuran, DMF = N,N-dimethylformamide, SiO_2 = silicon dioxide, NaOH = sodium hydroxide, DMSO = dimethylsulfoxide, °C = degrees Celsius, g = gram or grams, mg = milligram or milligrams, mm = millimeter, mL (or ml) = milliliter or milliliters, h = hour or hours, M = molar, N = normal, min = minute or minutes, MHz = megahertz, tlc = thin layer chromatography, v/v = volume to volume ratio, v/v/v = volume to volume to volume ratio and ca. = about.

"α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Example 1

N'-(3-Bromopyridin-2-yl)-1-(4-chlorophenyl)cyclopropanecarbohydrazide

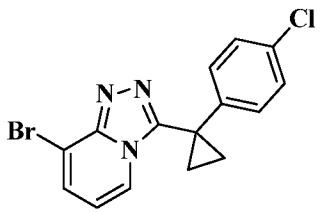


A mixture of 1-(4-chlorophenyl)cyclopropanecarboxylic acid (2.650 g, 13.48 mmol) and N-methylmorpholine (2.65 ml, 24.12 mmol) in 106 mL of THF was cooled to 0 °C. To this was added isobutyl chloroformate (2.212 ml, 16.85 mmol) dropwise over a period of 10 min. The mixture was allowed to stir at 0 °C for 1 h, and then a solution of 3-bromo-2-hydrazinylpyridine (3.17 g, 16.85 mmol) in 20 mL of THF was added. The reaction mixture was warmed to RT and stirred for 16 h. TLC analysis on silica gel using 5/95 (v/v) MeOH/ CH_2Cl_2 and LC/MS analysis showed the reaction to be completed. The reaction was quenched with water. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and

concentrated *in vacuo* to give a light brown solid. This solid was triturated with 1/1 (v/v) ether/hexane (2 x 4 mL) to remove some of the light brown color. The solvents were decanted and the resulting solid was dried under vacuum to give 4.5 g (82% yield) of a light yellow white solid. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 9.09 (d, J=2.0 Hz, 1H), 8.09 (dd, J=4.8, 1.5 Hz, 1H), 8.04 (d, J=2.0 Hz, 1H), 7.85 - 7.79 (m, 1H), 7.49 - 7.44 (m, 2H), 7.42 - 7.38 (m, 2H), 6.68 (dd, J=7.6, 4.7 Hz, 1H), 1.45 - 1.38 (m, 2H), 1.11 - 1.05 (m, 2H). LC/MS (ESI) 366.0/368.0/370.0 (M+1/M+3/M+5). The product was used with no further purification in the next step.

Example 2

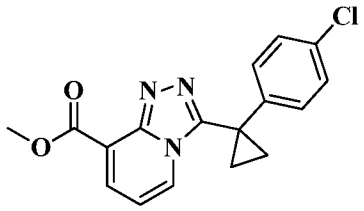
8-Bromo-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine



To N'-(3-bromopyridin-2-yl)-1-(4-chlorophenyl)cyclopropanecarbohydrazide (4.5 g, 12.27 mmol) in toluene (100 mL) was added $POCl_3$ (9.12 mL, 98.2 mmol). The yellow solution was refluxed for 2h. LC/MS analysis showed the presence of starting material still remained. The solution was refluxed for an additional 16 h which became a suspension. The suspension was cooled to 0 °C and poured into cold 1 N NaOH. Solid KOH was added till the pH was 8-9. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2CO_3. After filtration and concentration *in vacuo,* a white solid was obtained. The white solid was triturated with 1/1 (v/v) ether/hexane (2 x 10 mL). The solvents were decanted and the resulting solid was dried under vacuum to give 1.85 g (41.1% yield of white solid, 8-bromo-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine, ^{1}H NMR (CD_3OD, 500 MHz) δ 8.19 (dd, *J*=6.9, 0.8 Hz, 1H), 7.75 (dd, *J*=7.2, 0.8 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.17 - 7.12 (m, 2H), 6.89 (t, J=7.1 Hz, 1H), 1.72 - 1.67 (m, 2H), 1.66 - 1.62 (m, 2H). LC/MS (ESI) 348.0/350.0/352.0 (M+1/M+3/M+5).

Example 3

Methyl 3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carboxylate

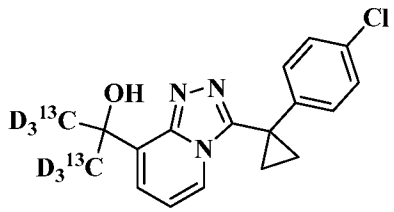


Using a pressure reactor manifold apparatus and a 75 mL glass pressure vessel, a mixture of 8-bromo-3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine (1.00 g, 2.87 mmol), palladium (II) acetate (0.064 g, 0.287 mmol), 1,3-bis(diphenylphosphino)propane (0.118 g, 0.287 mmol) and triethylamine (1.199 ml, 8.61 mmol) in MeOH (28.7 ml) with stirring under nitrogen was charged with approximately 25 psi CO (g). The reaction mixture was subjected to four freeze, pump, thaw cycles using a dry ice acetone bath and then pressurized with CO (g) to 25 psi. The mixture was heated to 50 °C with stirring overnight. The reaction mixture was cooled to RT and the system subjected to two freeze, pump, and thaw cycles to remove unreacted CO (g). HPLC and LC/MS analysis indicated the reaction was completed. TLC analysis on silica gel using 12.5/37.5/50.0 (v/v/v) MeOH/EtOAc/Hexane showed negligible starting material left. The crude reaction solution was combined with that of the same from another reaction and the solvent was removed *in vacuo* to obtain a dark brown/black viscous oil. The crude product was dissolved in CH_2Cl_2 (60 mL) and stirred with 50% sat. aqueous ammonium chloride (20 mL) for 30 min. The layers were separated and the CH_2Cl_2 was removed *in vacuo* to give 2.4956 g of the crude product. The crude product was purified by Flash Chromatography using a 120 g Isco silica gel column and eluting with a gradient from 5/15/80 (v/v/v) MeOH/EtOAc/hexane to 7.5/22.5/70 (v/v/v) MeOH/EtOAc/hexane and collecting 30 mL fractions. Fractions were analyzed by HPLC to determine which contained the desired product. Fractions 46 to 85 were pooled and the solvent removed *in vacuo to* give 1.6656 g (86 % yield) of yellow

foam. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (dd, *J*=7.0, 1.2 Hz, 1H), 7.99 (dd, *J*=6.7, 1.2 Hz, 1H), 7.28 - 7.20 (m, 2H), 7.07 - 7.01 (m, 2H), 6.84 (t, *J*=6.9 Hz, 1H), 4.09 (s, 3H), 1.75 - 1.69 (m, 2H), 1.59 - 1.53 (m, 2H). LC/MS (ESI) 328.1/330.1 (M+1/M+3).

Example 4

[($^{13}CD_3$)$_2$]2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol

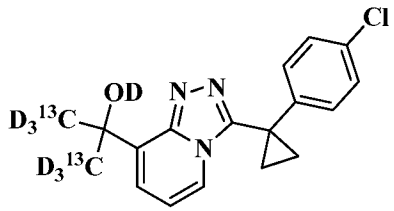


To an oven dried 50 ml round bottom flask with septum and stirbar was weighed magnesium (0.348 g, 14.33 mmol). To the flask was syringed anhydrous diethyl ether (10 mL). The reaction was cooled to 0 °C. To the flask was slowly added [$^{13}CD_3$] iodomethane (0.894 ml, 14.33 mmol). The reaction was stirred at RT for 2 h. To a separate 100 mL oven dried flask containing methyl 3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carboxylate (1.5656 g, 4.78 mmol) dissolved in anhydrous THF (30.8 ml) at 0 °C was cannulated the newly generated Grignard reagent. Anhydrous diethyl ether (7.0 mL) was used to rinse the Grignard production flask and the rinsings were also cannulated into the flask containing the ester. The reaction mixture was warmed to RT. After 90 min, HPLC and LC/MS analysis showed the reaction to be mostly complete. The reaction was cooled to 0 °C, brine (15.0 mL) was slowly added and the mixture was warmed to RT. The crude mixture was combined with that of the same from a reaction at approximately half the scale and the aqueous layer was extracted with EtOAc (5 x 50 mL). The combined organic extracts were washed with brine (10.0 mL) and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography using a 24 g Isco silica gel column using a gradient from 35/65 (v/v) EtOAc/hexane to 50/50 (v/v) EtOAc/hexane. The fractions containing pure product were pooled and the solvent was removed *in vacuo* to give 1.1694 g (49% yield) of a

pale yellow glass. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.07-7.99 (m, 1H), 7.42 (d, *J* =6.5 Hz, 1H), 7.37-7.30 (m, 2H), 7.14-7.06 (m, 2H), 6.94 (t, *J* =6.9 Hz, 1H), 1.65-1.51 (m, 4H). LC/MS (ESI) 336.3/338.3 (M+1/M+3).

Example 5

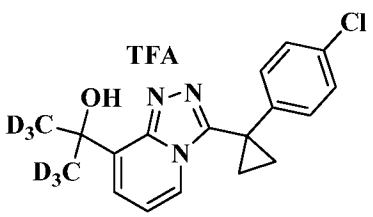
[(OD)($^{13}CD_3$)$_2$]2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol



To a roundbottom flask was transferred [($^{13}CD_3$)$_2$]2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol (1.1694 g, 3.45 mmol) and that of the same from a small scale practice reaction (91.6 mg, 0.273 mmol). To the flask was added CD_3OD (10 mL). After dissolving the material completely, the solvent was removed *in vacuo*. The solid was dissolved again in CD_3OD (10 mL) and the solvent removed *in vacuo* to give 1.1872 g (94% yield) of a pale yellow glass. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.07-8.00 (m, 1H), 7.41 (d, *J* =6.7 Hz, 1H), 7.37-7.28 (m, 2H), 7.15-7.04 (m, 2H), 6.93 (t, *J* =6.9 Hz, 1H), 1.57 (d, *J*=5.0 Hz, 4H). LC/MS (ESI) 336.3/338.3 (M+1/M+3). The deuterium on the oxygen exchanged back to a proton in the mobile phase of the LC.

Example 6

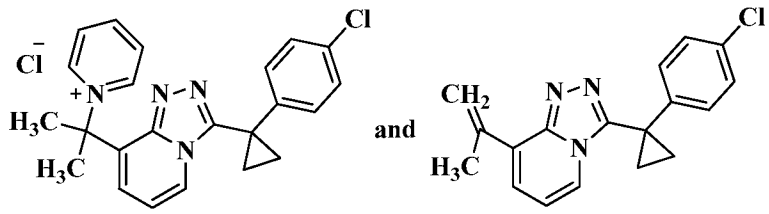
[(CD_3)$_2$]2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol trifluoroacetic acid salt



To a dry two neck flask with a stirbar was weighed methyl 3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridine-8-carboxylate (250.0 mg, 0.763 mmol). To this was syringed anhydrous diethyl ether (10.0 mL) and the mixture was stirred to dissolve the yellow solid. The flask was attached to a reflux condenser and methyl-D_3 magnesium iodide (1.678 mL, 1.678 mmol) in diethyl ether was added dropwise over 15 min. A solid formed upon the addition of the Grignard reagent and then slowly dissolved near the end of the addition of all of the solution. The reaction mixture was stirred at room temperature under nitrogen overnight. To the reaction was added methyl-D_3-magnesium iodide in diethyl ether (0.70 mL, 0.70 mmol) and the reaction was stirred at RT for an additional 2.5 h. The reaction mixture was cooled in an ice-water bath and 1M NH_4Cl (aq) (1.0 mL) was added dropwise over 15 min. The solution was warmed to RT and the layers were separated. The aqueous layer was extracted with EtOAc (6 x 10 mL). The combined organic extracts were washed with water (1 x 15 mL), brine (1 x 10 mL), dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to give a 150.3 mg of yellow brown oil. The crude product was dissolved in 2.0 mL of 0.1% TFA in acetonitrile and 1.0 mL of 0.1% TFA in water and was purified by semi-preparative HPLC on a Phenomenex LUNA C18, 21.1 mm x 250 mm column. Solvent A = 0.1% TFA in Water, Solvent B = 0.1% TFA in acetonitrile, Gradient: 0 min 30% B, 20 min 80% B, Flowrate = 20 ml/min, UV - 254 nm, Injection volume = 100 µl. The product with a retention time = 7.9 – 8.0 min. was collected, pooled and the solvent removed *in vacuo* to give a 33.2 mg of a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz,) δ 8.11 (d, *J*=6.8 Hz, 1H), 7.51 (d, *J*=6.6 Hz, 1H), 7.39 - 7.31 (m, 2H), 7.17 - 7.10 (m, 2H), 7.02 (t, *J*=6.8 Hz, 1H), 1.65 - 1.54 (m, 4H). ^{19}F NMR (376.46 MHz, DMSO-d_6) δ 74.45, 74.50 75.18. LC/MS (ESI) 333/335 (M+1/M+3).

Example 7

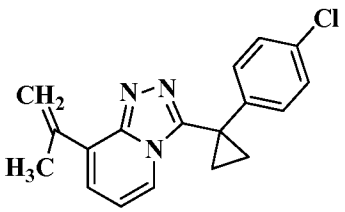
3-(1-(4-Chlorophenyl)cyclopropyl)-8-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridine and 1-(2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-yl)pyridin-1-ium chloride



To a round bottom flask was weighed 2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol hydrochloride, (200 mg, 0.499 mmol). To this was added pyridine (0.764 ml) and the solution was cooled to 0 °C followed by the slow addition of phosphorus oxychloride (0.233 ml, 2.495 mmol) over 10 min with stirring. The mixture was stirred at 0 °C for 10 min and then heated to 60 °C for 2 h. The reaction mixture was cooled to RT and solvent removed *in vacuo*, chilled to 0 °C, CH_2Cl_2 (4 ml) was added to the pasty white residue then H_2O (1.0 ml) was carefully added. To the solution was added solid sodium carbonate to adjust the pH to ~ 8 by pH paper. The aqueous layer was extracted with CH_2Cl_2 (5 x 4 ml), EtOAc (2 x 4 ml) and CH_2Cl_2 (2 x 4 ml). The combined organic extracts were concentrated *in vacuo* to give 241.5 mg of a viscous yellow liquid. The crude product was purified by Flash Chromatography using an Isco 4 g silica gel column, eluting with a gradient 0/100 (v/v) MeOH/CH_2Cl_2 to 3/97 (v/v) MeOH/CH_2Cl_2 and then with 10/90 (v/v) MeOH/ CH_2Cl_2 to elute the more polar pyridine adduct. Fractions of 15 ml were collected. Fractions containing the alkene product were pooled and the solvent removed *in vacuo* to give 76.4 mg (49.4% yield) of an off-white solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.07 (dd, *J*=6.9, 0.7 Hz, 1H), 7.40-7.36 (m, 1H), 7.35-7.29 (m, 2H), 7.10-7.04 (m, 2H), 6.97 (t, *J* =6.9 Hz, 1H), 6.78 (d, *J*=2.1 Hz, 1H), 5.59 (s, 1H), 2.24 (d, *J*=0.6 Hz, 3H), 1.60 (d, *J*=3.2 Hz, 4H). LC/MS (ESI) 310.2/312.2. Fractions containing the pyridine adduct were combined and solvent removed in *vacuo* to give 122.2 mg of a viscous pale yellow oil. ^{1}H NMR (DMSO-d_6, 300 MHz) d 9.22 (d, *J*=5.9 Hz, 1H), 8.59 (t, *J*=7.8 Hz, 1H), 8.33-8.24 (m, 1H), 8.08 (t, *J*=7.2 Hz, 3H), 7.78-7.67 (m, 1H), 7.38-7.26 (m, 2H), 7.20-7.04 (m, 3H), 2.28 (s, 6H), 1.51 (d, *J*=6.5 Hz, 4H). LC/MS (ESI) 310.3/312.2 (M+1/M+3) was detected from the loss of pyridine to form the tertiary and benzylic carbocation.

Example 8

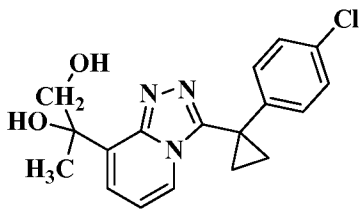
3-(1-(4-Chlorophenyl)cyclopropyl)-8-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridine



To a 1 ml vial was weighed 1-(2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-yl)pyridin-1-ium chloride (15.7 mg, 0.040 mmol) in anhydrous toluene (0.403 ml) under nitrogen at RT. The reaction was stirred for 5 h at 100 °C and then cooled to RT overnight. The toluene was removed *in vacuo* to obtain 13.6 mg of a pale yellow solid. To the solid was added water (0.50 ml). The aqueous solution was extracted with EtOAc (4 x 0.5 ml). The EtOAc extracts were pooled and the solvent was removed *in vacuo* to give 5.8 mg (46.5% yield) of a pale yellow oily solid. ^{1}H NMR (CD_3OD, 400 MHz) d 8.07 (d, *J*=6.8 Hz, 1H), 7.39 (d, *J* =7.0 Hz, 1H), 7.30-7.25 (m, 2H), 7.14-7.08 (m, 2H), 6.96 (t, *J* =7.0 Hz, 1H), 6.36 (s, 1H), 5.56 (s, 1H), 2.28 (s, 3H), 1.69-1.59 (m, 4H). LC/MS (ESI) 310.33/312.25 (M+1/M+3).

Example 9

2-(3-(1-(4-Chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propane-1,2-diol

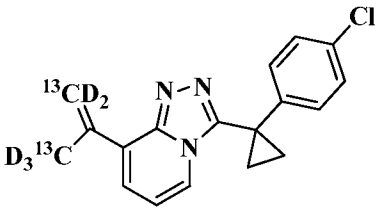


To a solution of 3-(1-(4-chlorophenyl)cyclopropyl)-8-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (127 mg, 0.410 mmol) in acetone (3.727 ml) and water (0.373 ml) was added 4-methylmorpholine 4-oxide hydrate (117 mg, 0.820 mmol) and 2.5% Osmic acid (0.257 ml, 0.020 mmol) at 0 °C. The reaction was allowed to

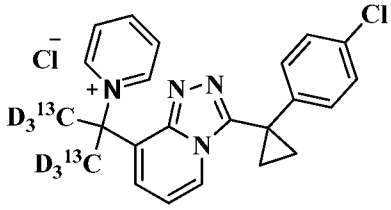
slowly warm to RT and then stirred overnight. The solvent was removed *in vacuo* to give a residue which was purified by Flash Chromatography using a 12 g Isco column and a gradient from 0/100 (v/v) MeOH/CH_2Cl_2 to 2.5/97.5 (v/v) MeOH/CH_2Cl_2. Fractions of 25 ml were collected. Pure fractions were combined and the solvent was removed *in vacuo* to give 104.1 mg (73.9% yield) of a pale yellow viscous oil. ^{1}H NMR (DMSO-d_6, 300 MHz) d 8.05 (dd, *J*=6.7, 1.2 Hz, 1H), 7.43 (dd, *J* =6.9, 1.0 Hz, 1H), 7.37-7.30 (m, 2H), 7.15-7.08 (m, 2H), 6.95 (t, *J* =6.9 Hz, 1H), 4.62 (t, *J*=6.2, Hz, 1H), 4.10 – 3.98 (m, 2H), 3.78 (dd, *J*=10.9, 5.9 Hz, 1H) 1.59 (d, *J*=11.7 Hz, 7H). LC/MS (ESI) 344.33/346.25 (M+1/M+3).

Examples 10a and 10b

[$^{13}CD_3$ $^{13}CD_2$]3-(1-(4-chlorophenyl)cyclopropyl)-8-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridine and [($^{13}CD_3$)$_2$]1-(2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-yl)pyridin-1-ium chloride



and

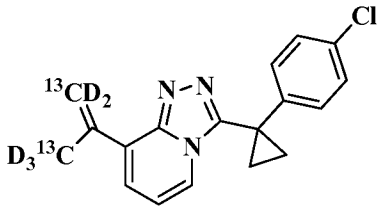


To a round vbottom flask with stirbar was weighed [(OD)($^{13}CD_3$)$_2$]2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-ol (0.5615 g, 1.667 mmol). To this was added pyridine (2.55 ml). The reaction was cooled to 0 °C and phosphorous (V) oxychloride (0.775 ml, 8.33 mmol) was added dropwise over 10 min. The mixture was stirred at 0° C for 10 min then heated to 60 °C for 40 min. HPLC and LC/MS analysis showed the reaction to be nearly completed. The crude reaction mixture was combined with that of the same from another synthesis of nearly the same scale and was cooled to 0 °C. To this was added CH_2Cl_2 (30 mL) and H_2O (7.0 mL) carefully over 15 min. Solid sodium carbonate was carefully added to adjust the pH to ~ 8 using pH paper. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 x 30 mL). The solvent from the combined organic extracts

was removed *in vacuo* to give 1.5582 g of a viscous brown oil. The crude product was purified by Flash Chromatography using an Isco 24 g silica gel column using gradient elution from 0/100 (v/v) MeOH/CH_2Cl_2 to 3/97 (v/v) MeOH/CH_2Cl_2 and collecting 28 mL fractions. Fractions 28-32 were pooled and solvent removed *in vacuo* to give 274 mg of a viscous yellow oil that was a mixture of 30% starting material and 70% desired product as determined by HPLC analysis. Fractions 9-27 were also pooled and the solvent removed *in vacuo* to give 110.8 mg of a viscous yellow oil that was a mixture of 84% starting material and 16% desired product as determined by HPLC analysis. A more polar product eluted from the column using a gradient starting with 10/90 (v/v) MeOH/CH_2Cl_2 to 20/80 (v/v) MeOH/CH_2Cl_2 to give 707.9 mg of a product that was identified as the pyridine adduct salt [($^{13}CD_3$)$_2$]1-(2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-yl)pyridin-1-ium chloride. The 274 mg sample was repurified by Flash Chromatography using an Isco 24 g silica gel column eluting with a gradient from 5/95 (v/v) EtOAc/hexane to 25/75 (v/v) EtOAc/hexane and collecting 28 mL fractions. Fractions containing the product were pooled and solvent removed *in vacuo* to give 134.7 mg (12.4% yield) of an off white solid. Likewise, the 110.8 mg sample was repurified by Flash Chromatography using an Isco 12 g silica gel column eluting with a gradient from 5/95 (v/v) EtOAc/hexane to 25/75 (v/v) EtOAc/hexane and collecting 20 mL fractions. Fractions containing the product were pooled and solvent removed *in vacuo* to give 38.9 mg (3.6% yield) of an off white solid. Both desired products had nearly the same NMR and LC/MS spectra. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.06 (d, *J*=6.2 Hz, 1H), 7.37 (d, *J* =7.0 Hz, 1H), 7.34-7.29 (m, 2H), 7.08-7.03 (m, 2H), 6.96 (t, *J* =6.9 Hz, 1H), 1.64-1.53 (m, 4H). LC/MS (ESI) 317.3/319.2 (M+1/M+3). The more polar product that eluted later from the first Flash Chromatography column was identified as [($^{13}CD_3$)$_2$]1-(2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-yl)pyridin-1-ium chloride ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.20 (d, *J*=5.9 Hz, 1H), 8.58 (t, *J*=7.6 Hz, 1H), 8.28 (s, 1H), 8.08 (t, *J*=7.2 Hz, 3H), 7.70 (d, *J*=6.7 Hz, 1H), 7.37-7.26 (m, 2H), 7.22-6.97 (m, 3H), 1.63-1.40 (m, 4H). LC/MS (ESI) 318.3/320.3 (M+1/M+3) from loss of the pyridine to form the stabilized tertiary and benzylic carbocation.

Example 11

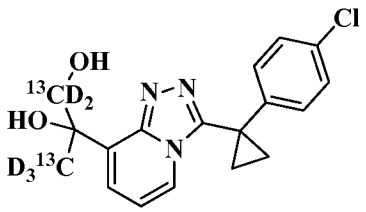
[$^{13}CD_3$ $^{13}CD_2$]3-(1-(4-chlorophenyl)cyclopropyl)-8-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridine



To a 25 mL roundbottom flask was weighed [($^{13}CD_3$)$_2$]1-(2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propan-2-yl)pyridin-1-ium chloride (248.6 mg, 0.574 mmol) under a nitrogen To this was syringed DIPEA (0.327 mL, 1.874 mmol) and the mixture was stirred at RT for 30 min. Anhydrous toluene (6.25 mL) was added and the mixture was stirred at 100 °C for 24 h. The reaction mixture was cooled to RT and solvent removed *in vacuo*. To the crude mixture was added EtOAc (10 mL) and brine (5 mL). The layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL). The solvent from the combined EtOAc extracts was removed *in vacuo* to obtain 206.4 mg of viscous tan oil. The crude product was combined with that of the same from another reaction at 1.24 times the scale. The combined crude products were purified by Flash Chromatography using a 24 g Isco column and gradient from 20/80 (v/v) EtOAc/hexane to 30/70 (v/v) EtOAc/hexane to give 308.6 mg (75.9% yield) of a colorless oil. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.08 (d, *J*=6.8 Hz, 1H), 7.40 (d, *J* =7.0 Hz, 1H), 7.32-7.26 (m, 2H), 7.15-7.09 (m, 2H), 6.97 (t, *J* =7.0 Hz, 1H), 1.69-1.61 (m, 4H). LC/MS (ESI) 317.3/319.3 (M+1/M+3).

Example 12

[$^{13}CD_3$ $^{13}CD_2$]2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propane-1,2-diol



To a solution of [$^{13}CD_3$ $^{13}CD_2$]3-(1-(4-chlorophenyl)cyclopropyl)-8-(prop-1-en-2-yl)-[1,2,4]triazolo[4,3-a]pyridine (136 mg, 0.429 mmol) in acetone (3.9 mL) and water (0.390 mL) at 0 °C was added 4-methylmorpholine 4-oxide hydrate (122 mg, 0.859 mmol) and 2.5% Osmium tetraoxide (0.267 mL, 0.021 mmol). The reaction was warmed to RT and stirred overnight. The crude reaction mixture was combined with that of the same from another reaction at 1.74 times the scale. The crude reaction was purified by Flash Chromatography using a 24 g Isco silica column and gradient from 0/100 (v/v) MeOH/CH_2Cl_2 to 2.5/97.5 (v/v) MeOH/CH_2Cl_2 collecting 25 mL fractions. Pure fractions were combined and the solvent removed *in vacuo* to give 280.8 mg of a pale yellow viscous oil/glass. This oil/glass was dissolved in CH_2Cl_2 and the CH_2Cl_2 was removed *in vacuo*. This was repeated three additional times to give 268.6 mg (65% yield) of [$^{13}CD_3$ $^{13}CD_2$]2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propane-1,2-diol as a pale brown foam. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.06 (d, *J*=5.9 Hz, 1H), 7.57 (d, *J* =6.7 Hz, 1H), 7.38-7.22 (m, 2H), 7.18-7.07 (m, 2H), 6.96 (t, *J* =6.9 Hz, 1H), 1.74-1.53 (m, 4H). LC/MS (ESI) 351.3/353.3 (M+1/M+3)

ASSAY(S) FOR 11-BETA-HYDROXYSTEROID DEHYDROGENASE ACTIVITY

The *in vitro* inhibition of recombinant human 11beta-HSD1 can be determined as follows.

[^{3}H]-Cortisone with a specific radioactivity of 50 Ci/mmol (ART 743, Lot: 050906) is from American Radiolabeled Chemicals, Inc. (St Louis, MO); monoclonal ab to Cortisol (P01-9294M-P, Lot: L-28) is from East Coast Bio., (North Berwick, ME); Protein A-yttrium silicate, type-1, SPA bead NJ® (RPN-143) is from Amersham LifeSciences, (Piscataway, NJ); 384 well-Optiplate384® (#6007299) is from PerkinElmer (Boston, MA); DPBS, pH 7.4 (14040) is from GIBCO, (Grand Island, NY); carbenoxolone (C4790) is from Sigma, (St Louis, MO).

Full length recombinant human 11β-HSD1 cDNAs and the cDNA encoding human 11β-HSD2 are expressed stably in HEK 293 EBNA cells. Cells are grown in DMEM (high glucose) containing MEM non-essential amino acids, L-glutamine, hygromycin B (200 μg/ml), and G-418(200 μg/ml) in the presence of 10% FBS.

Human 11β-HSD1 transfected HEK 293 EBNA cells are grown to 80% confluency and the cell pellet is quick frozen and stored at -80 °C before purification. Cell paste, 40 g from –80 °C storage, is thawed in water and then 100 ml of homogenization buffer H (0.01 M sodium phosphate pH 6.5 containing 0.25 M sucrose) and protease inhibitor cocktail (Roche #1836145 1 tablet per 50 ml) are added to completely thaw the paste. The cell paste suspension is homogenized using a Polytron for 20 seconds to create a homogeneous mixture. Additional buffer H is added to a volume of 300 ml and cells are broken open using a N2-bomb (at 4°C) in two batches by treating at 500 psi. The extract is centrifuged at 750 X g for 30 min. The supernatant is centrifuged at 20,000 X g for 30 min. The supernatant is further centrifuged at 105,000 X g for 60 min. The 105,000 X g pellet is resuspended in buffer H and centrifuged at 105,000 X g for 60 min. The microsome pellet is scraped from the bottom of tube and resuspended in 0.01M phosphate buffer, pH 6.5 containing protease inhibitors (Roche #1836145, 1 tablet per 50 ml). Aliquots are

stored at -80 °C until needed. The protein concentration is measured by the BioRad method using BSA standard.

Compounds are dissolved in DMSO to obtain 10 mM stock concentrations. From the 10 mM stock, the compounds are diluted in DMSO to achieve the concentrations.

11β-HSD1 SPA Enzyme Assay

11β-HSD1 is assayed by Scintillation Proximity assay in a 384-well Perkin Elmer white plate. The dose response of the compounds is determined using 11 half-log dilutions of compound in DMSO in duplicate. To each well, 0.5 µl of compound dilution in DMSO are added. 15 µl of assay buffer (for blanks) or 15 µl of human microsomes in assay buffer are added next and the plates are incubated for 10 min at room temperature. The final microsomal protein concentration is 1.1 µg/assay. Duplicates are in the same plate one row below the other. 10 µl of ^{3}H-cortisone (final concentration 40 nM) is added to each well and the plate is spun down to mix and brings down the contents to the bottom of the wells. The plates are incubated at room temperature with gentle shaking for 4 hrs. The reaction is stopped with addition of 10 µl of 10 mM carbenoxolone. Then, 0.5 mg of yttrium silicate SPA beads coupled to anti-cortisol antibody in 20 µl are added to all the wells of plate, which are spun down once more and incubated at room temperature overnight. The plate is read in a TopCount® (1 min/well). Data are uploaded automatically to Tool Set, a Lead Evaluation informatics program for data capture and calculation. Graphs are generated with the Curve Master program.

The *in vivo* inhibition of recombinant human 11beta-HSD1 can be determined as follows.

Studies are conducted utilizing diet induced obese (DIO) mice obtained from Jackson Laboratory (ME, USA). These mice are fed a 60% fat diet (Research Diets D12492) soon after weaning and kept on this diet for 24 weeks. These mice are individually housed. All mice are housed under controlled temperature (23°C) and lighting (12 hours of light between 6 am to 6 pm, 12 hours of dark) with free access to

water. The animals continued on this diet and are utilized for experimentation at 30 to 32 weeks of age, at which time these mice should weigh 45 to 55 grams.

The basic model of 11-dehydrocorticosterone (DHC) administration to mice to produce corticosterone has been reported in the literature for clinical and preclinical evaluation of the activity of 11β-HSD. Essentially DHC (Steraloids Inc., Newport RI), is suspended in the vehicle at a concentration of 10 mg/kg in a volume of 7.5 ml/kg of mouse body weight. For a typical study, non-fasting mice are weighed and separated into groups (n=6) where body weights are not statistically different from each other. Animals are bled via a tail knick, for a 0 time sample and then dosed orally (7.5 ml/kg) with vehicle or drug. At 60 minutes post administration of vehicle or compound, mice are bled again via the tail tip and dosed orally (7.5 ml/kg) with DHC 10mg/kg. All animals are subsequently bled at 30, 60 and 120 minutes post DHC dosing. Thirty- five microliters of whole blood are collected per time point in microvette tubes coated with EDTA (Sarstedt Tubes Microvette CB 300/ Haematology Potassium EDTA # 16.444.300) and kept on ice. Samples are centrifuged at 4 °C in a Beckman Coulter centrifuge for 10 minutes at 2500 RPM. Plasma is separated and collected and immediately frozen at –20 °C until corticosterone analysis can be assessed.

Plasma Corticosterone is measured using an EIA (IDS AC-14F1). Samples are measured at (1:2) for the -30(or -60 minute) and 0 time point and (1:10) for the 30, 60 and 120 minutes time points. AUC is calculated using Graphpad and the zero timepoint is used as the baseline. One way ANOVA is calculated using Sigmastat. A p value of less than 0.05 via post hoc analysis with Dunnett's is used to determine statistical significance.

The vehicle utilized for the suspension of the compounds is 0.5% methocel; 0.1% tween 80 in water. Methocel Cellulose (M-0262) is purchased from Sigma-Aldrich, St Louis, MO 6. Tween 80 (274364) is purchased from Sigma-Aldrich, St Louis, MO. Compounds are administered in 7.5 ml/kg volumes at final dosages of 0.1 to 300 mg/kg depending on the study and compound evaluated.

Metabolic Stability

The formation rate of hydroxylated metabolites of compounds of the present invention were determined as follows:

Test compounds were incubated with pooled human liver microsomes ("HLM", BD Ultrapool, Cat. # 452117). The incubation mixtures (1 mL) contained phosphate buffer (0.1 M, pH 7.4), $MgCl_2$ (10 mM), HLM (2 mg protein/mL), N-nicotinamide adenine dinucleotide phosphate sodium ("NADPH", reduced form, 2 mM), and test compounds (3 or 10 μM). The final organic solvent in incubations was <1% (v/v). Reactions were initiated with the addition of NADPH and the mixtures were incubated at 37°C with shaking (90 rpm). 200 μL of reaction solution was collected at 0, 0.5, 1, and 2 hours ("h").

Similarly, the test compounds were also incubated with cDNA expressed cytochrome P450 enzyme ("CYP2C19", BD Genetest, Cat. #456259). The incubation mixtures (1 mL) contain phosphate buffer (0.1 M, pH 7.4), $MgCl_2$ (10 mM), CYP2C19 (0.05 μM), NADPH (2 mM), and test compound (3 or 10 μM). Similar to the procedure described above, the reactions were initiated with the addition of NADPH and the mixtures were incubated at 37°C with shaking (90 rpm). 200 μL of reaction solution was collected at 0, 0.5, 1, and 2 h.

Ice-cold acetonitrile (200 μL) containing clozapine (200 nM, used as mass spectrometry internal standard) was then added to the incubation solution to stop the reaction. After centrifugation at 13,000 rpm for 10 minutes, the supernatant was collected for LC-MS analysis.

Hydroxlyated reference standards, 2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propane-1,2-diol and [$^{13}CD_3$ $^{13}CD_2$]2-(3-(1-(4-chlorophenyl)cyclopropyl)-[1,2,4]triazolo[4,3-a]pyridin-8-yl)propane-1,2-diol, were synthesized for the quantitation of hydroxylated metabolites. Reference standard solutions were prepared by mixing the reference standards with blank HLM or CYP2C19 incubation solution (0.1 M, pH7.4 phosphate buffer; 10 mM MgCl2; 2 mg/ml HLM or 0.05 μM CYP2C19). Similar to the procedure described above, ice-cold acetonitrile (200 μL) containing clozapine (200 nM) was added to 180 μL of the

solution and the mixture was centrifuged at 13,000 rpm for 10 min. Supernatant was collected and 20 μL of 20 mM NADPH was added (final concentration 2 mM). The resulting solutions were analyzed by LC-MS in the same manner as the test compound solutions. The final concentrations of reference standards were 5, 1, 0.5, 0.1, 0.05, 0.01 and 0.005 μM.

Metabolite quantitation was performed with an LC-MS system comprised of a Shimadzu LC-10AD high-performance liquid chromatograph system (Shimadzu Scientific Instruments, Columbia, MD), a LEAP Technologies autoinjector (CTC Analytics, Switzerland), and a Sciex Q-Trap 4000 mass spectrometer (Applied Biosystems, Ontario, Canada). Samples (25 μL) were injected onto a Waters C18 column (5 μm, 2.1 x 150 mm, Part# 186001301). The mobile phases and HPLC gradient was as follows:

Total Time (min)	**Flow rate (μl/min)**	**Water with 0.1% formic acid**	**100% acetonitrile**
0	300	95	5
2	300	95	5
30	300	60	40
32	300	10	90
35	300	10	90
36	300	95	5
40	300	95	5

HPLC elute was introduced into a Sciex Q-Trap 4000 mass spectrometer, which was equipped with an electrospray ionization source operating at positive-ion mode with a capillary temperature of 300°C and spray voltage of 5.5 kV. Ultra high purity nitrogen gas was used as the curtain gas, ion source gas, and collision gas. The gas flow and declustering potential (DP) voltage and other voltages were adjusted to provide maximum sensitivity for the parent compound and metabolite standard. The compounds of interest, metabolites and IS were separated by specific MRM transitions with minimal or no cross-interference.

Concentrations (nM) of metabolites of compounds of the present invention following HLM and CYP2C19 incubation were determined based on the standard curves of the hydroxlated reference standards. Since the peak area ratios of reference standards to clozapine are approximately the same at equal standard concentrations, concentrations (nM) of one reference standard following HLM and CYP2C19 incubation were calculated based on the standard curve of the other reference standard. The formation rates of hydroxylated metabolites for the tested compounds were determined in 1 h since their formations were linear from 0 to 1 h at both 3 and 10 μM.

Find below in Tables 1 and 2 data for compared compounds (See WO 2009/045753 A1). Generally, the comparative data shows the unexpected improvement in metabolic stability of the compounds of the present invention.

Table 1

Concentration of hydroxylated metabolites following HLM and CYP2C19 incubation

		Hydroxylated metabolite (nM)					
		HLM Incubation			CYP2C19 Incubation		
Incubation Time	Substrate Concentration	Example 1 WO 2009/045753 A1	Example 4 Present Invention	Example 6 Present Invention	Example 1 WO 2009/045753 A1	Example 4 Present Invention	Example 6 Present Invention
0h	3 μM	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	10 μM	3.65	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
0.5h	3 μM	44.27	6.28	5.58	218.96	29.22	26.87
	10 μM	125.31	14.12	11.36	566.35	67.48	56.61
1h	3 μM	68.23	8.62	7.32	416.36	51.39	43.79
	10 μM	199.06	19.98	15.90	977.22	116.83	98.35
2h	3 μM	86.98	10.40	8.60	590.26	82.04	66.39
	10 μM	274.48	27.06	21.84	1548.96	159.00	159.00

<LOQ: below limit of quantitation

Table 2

Formation rate of hydroxylated metabolites following HLM and CYP2C19 incubation

	Hydroxylated metabolite formation rate					
	HLM Incubation (nmol/(h*mg protein))			CYP2C19 (nmol/(h*nmol enzyme))		
Substrate Concentration	Example 1 WO 2009/045753 A1	Example 4 Present Invention	Example 6 Present Invention	Example 1 WO 2009/045753 A1	Example 4 Present Invention	Example 6 Present Invention
3 μM	32.29	2.78	2.13	8.26	0.92	0.77
10 μM	97.71	8.46	6.42	19.46	2.23	1.86

Surprisingly, it was discovered that the compounds of the present invention possess beneficial pharmacological characteristics, such as, metabolic stability in comparison to compounds know in the art. See Tables 1 and 2. For example, the concentration (nM) of hydroxylated metabolite of Example 1 of WO 2009/045753 A1 was 7~11 fold higher than those of the hydroxlated metabolites of Examples 4 and 6 of the present invention at different substrate concentrations (3 and 10 μM).

UTILITIES AND COMBINATIONS

A. Utilities

The compounds of the present invention possess activity as inhibitors of the enzyme 11-beta-hydroxysteroid dehydrogenase type I, and, therefore, may be used in the treatment of diseases associated with 11-beta-hydroxysteroid dehydrogenase type I activity. Via the inhibition of 11-beta-hydroxysteroid dehydrogenase type I, the compounds of the present invention may preferably be employed to inhibit or modulate glucocorticoid production, thereby interrupting or modulating cortisone or cortisol production.

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, treating, preventing, or slowing the progression of diabetes and related conditions, microvascular complications associated with diabetes, macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, inflammatory diseases and other maladies. Consequently, it is believed that the compounds of the present invention may be used in preventing, inhibiting, or treating diabetes, hyperglycemia, impaired glucose tolerance, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae (acute coronary syndrome, myocardial infarction, angina pectoris, peripheral vascular disease, intermittent claudication), abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, non-cardiac ischemia, infection, cancer, vascular restenosis,

pancreatitis, neurodegenerative disease, lipid disorders, cognitive impairment and dementia, bone disease, HIV protease associated lipodystrophy, glaucoma and inflammatory diseases, such as, rheumatoid arthritis, Cushing's Disease, Alzheimer's Disease and osteoarthritis.

Metabolic Syndrome or "Syndrome X" is described in Ford et al., *J. Am. Med. Assoc.*, 287:356-359 (2002) and Arbeeny et al., *Curr. Med. Chem. - Imm., Endoc. & Metab. Agents*, 1:1-24 (2001).

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, Ia, Ib, Ic, Id, Ie, If, Ig or II, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), *e.g.*, an antidiabetic agent or other pharmaceutically active material.

The compounds of the present invention may be employed in combination with one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents, anti-hyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-atherosclerotic agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, appetite suppressants, treatments for heart failure, treatments for peripheral arterial disease and anti-inflammatory agents.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include insulin and insulin analogs (*e.g.*, LysPro insulin, inhaled formulations comprising insulin); glucagon-like peptides; sulfonylureas and analogs (*e.g.*, chlorpropamide, glibenclamide, tolbutamide, tolazamide, acetohexamide, glypizide, glyburide, glimepiride, repaglinide, meglitinide); biguanides (*e.g.*, metformin, phenformin, buformin); alpha2-antagonists

and imidazolines (*e.g.*, midaglizole, isaglidole, deriglidole, idazoxan, efaroxan, fluparoxan); other insulin secretagogues (*e.g.*, linogliride, insulinotropin, exendin-4, N,N-dimethyl-N′-[2-(4-morpholinyl)phenyl]guanidine (E)-2-butenedioate salt (BTS-675820), (-)-N-(*trans*-4-isopropylcyclohexanecarbonyl)-D-phenylalanine (A-4166)); thiazolidinediones and PPAR-gamma agonists (*e.g.*, ciglitazone, pioglitazone, troglitazone, rosiglitazone); PPAR-alpha agonists *e.g.*, fenofibrate, gemfibrozil); PPAR alpha/gamma dual agonists (*e.g.*, muraglitazar, peliglitazar, aleglitazar); SGLT2 inhibitors (*e.g.*, 3-(benzo[b]furan-5-yl)-2′,6′-dihydroxy-4′-methylpropiophenone-2′-O-(6-O-methoxycarbonyl)-β-d-glucopyranoside (T-1095 Tanabe Seiyaku), phlorizin, TS-033 (Taisho), dapagliflozin (BMS), sergiflozin (Kissei), AVE 2268 (Sanofi-Aventis)), canagliflozin; 11-beta-hydroxysteriod dehydrogenase type I inhibitors (*e.g.*, AMG221, INCB13739); dipeptidyl peptidase-IV (DPP4) inhibitors (*e.g.*, saxagliptin, sitagliptin, vildagliptin, alogliptin, linagliptin, dutogliptin and denagliptin); glucagon-like peptide-1 (GLP-1) receptor agonists (*e.g.*, Exenatide (Byetta), NN2211 (Liraglutide, Novo Nordisk), AVE0010 (Sanofi-Aventis), R1583 (Roche/Ipsen), SUN E7001 (Daiichi/Santory), GSK-716155 (GSK/Human Genome Sciences) and Exendin-4 (PC-DACTM); aldose reductase inhibitors (*e.g.*, those disclosed in WO 99/26659); RXR agonists (*e.g.*, reglitazar (JTT-501), 5-[[6-[(2-fluorophenyl)methoxy]-2-naphthalenyl]methyl]- 2,4-thiazolidinedione (MCC-555), 5-[[3-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)-4-(trifluoromethoxy)-phenyl]methylene]-2,4-thiazolidinedione (MX-6054), DRF2593, farglitazar, (±)-5-[(2,4-dioxothiazolidin-5-yl)methyl]-2-methoxy-N-[[(4-trifluoromethyl)phenyl]-methyl]benzamide (KRP-297), 6-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)cyclopropyl]-3-pyridinecarboxylic acid (LG100268)); fatty acid oxidation inhibitors (*e.g.*, clomoxir, etomoxir; α-glucosidase inhibitors: precose, acarbose, miglitol, emiglitate, voglibose, 2,6-dideoxy-2,6-imino-7-O-β -D-glucopyranosyl-D-glycero-L-gulo-heptitol (MDL-25,637), camiglibose); beta-agonists (*e.g.*, methyl ester [4-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenoxy]-acetic acid (BRL 35135), 2-[4-[(2S)-2-[[(2S)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]phenoxy]-acetic acid (BRL 37344), 4-[(3R)-3-[bis[(2R)-2-hydroxy-2-phenylethyl]amino]butyl]-benzamide (Ro 16-8714), 2-[4-[2-[[(2S)-2-hydroxy-3-phenoxypropyl]amino]ethoxy]phenoxy]-N-(2-

methoxyethyl)-acetamide (ICI D7114), 5-[(2R)-2-[[(2R)-2-(3-chlorophenyl)-2-hydroxyethyl]amino]propyl]-3-benzodioxole-2,2-dicarboxylic acid, disodium salt (CL 316,243), TAK-667, AZ40140); phosphodiesterase inhibitors, both cAMP and cGMP type (*e.g.*, sildenafil, 9-((1S,2R)-2-fluoro-1-methylpropyl)-2-methoxy-6-(1-piperazinyl)purine hydrochloride (L-686398), L-386,398); amylin agonists (*e.g.*, pramlintide); lipoxygenase inhibitors (*e.g.*, masoprocal); somatostatin analogs (*e.g.*, lanreotide, seglitide, octreotide); glucagon antagonists (*e.g.*, BAY 276-9955); insulin signaling agonists, insulin mimetics, PTP1B inhibitors (*e.g.*, 2-[2-(1,1-dimethyl-2-propenyl)-1H-indol-3-yl]-3,6-dihydroxy-5-[7-(3-methyl-2-butenyl)-1H-indol-3-yl]-2,5-cyclohexadiene-1,4-dione (L-783281), TER17411, TER17529); gluconeogenesis inhibitors (*e.g.*, GP3034); somatostatin analogs and antagonists; antilipolytic agents (*e.g.*, nicotinic acid, acipimox, N-cyclohexyl-2′-O-methyl-adenosine (WAG 994)); glucose transport stimulating agents (*e.g.*, 4-chloro-α-[(4-methylphenyl)sulfonyl]-benzeneheptanoic acid (BM-130795)); glucose synthase kinase inhibitors (*e.g.*, lithium chloride, CT98014, CT98023); galanin receptor agonists; Chemokine receptor antagonist CCR2/5 (*e.g.*, NCB3284, MK-0812, INCB8696, maraviroc (Pfizer) and vicriviroc); thyroid receptor agonists (*e.g.*, KB-2115 (KaroBio)); glucokinase activators (*e.g.*, RO-27-4375, RO-28-1675 (Roche), 6-[[3-[(1S)-2-methoxy-1-methylethoxy]-5-[(1S)-1-methyl-2-phenylethoxy]benzoyl]amino]-3-pyridinecarboxylic acid (GKA-50 AstraZeneca)); GPR40 modulators (*e.g.*, (S)-4-(dimethylamino)-3-(4-((4-methyl-2-p-tolylthiazol-5-yl)methoxy)phenyl)-4-oxobutanoic acid, 6-chloro-2-(4-chlorobenzylthio)-1-(4-(methoxymethoxy)phenyl)-1H-benzo[d]imidazole, TAK-875, CNX011, and P1736); GPR119 modulators (*e.g.*, MBX-2987, PSN-821,ZYG-19,DS-8500, AR7947); and GPR120 modulators (*e.g.*, Compound 43 from *J. Med. Chem.*, **2012**, *55*, 4511-4515).

Examples of suitable lipid lowering agents and anti-atherosclerotic agents for use in combination with the compounds of the present invention include one or more MTP/ApoB secretion inhibitors (*e.g.*, dirlopatide, N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4′-(trifluoromethyl)[1,1′-biphenyl]-2-yl] carbonyl-]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, methanesulfonate, CP-741952 (Pfizer), SLx-4090 (Surface Logix)); HMG CoA reductase inhibitors (*e.g.*, atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin); squalene synthetase inhibitors, PPAR alpha

agonists and fibric acid derivatives (*e.g.*, fenofibrate, gemfibrozil); ACAT inhibitors; lipoxygenase inhibitors; cholesterol absorption inhibitors (*e.g.*, ezetimibe); thyroid receptor agonists (*e.g.*, as set forth above); Ileal Na+/bile acid cotransporter inhibitors (*e.g.*, compounds as disclosed in *Drugs of the Future*, 24:425-430 (1999); upregulators of LDL receptor activity (*e.g.*, (3R)-3-[(13R)-13-hydroxy-10-oxotetradecyl]-5,7-dimethoxy-1(3H)-isobenzofuranone (Taisho Pharmaceutical Co. Ltd.) and (3α,4α,5α)-4-(2-propenyl)-cholestan-3-ol (Eli Lilly); bile acid sequestrants (*e.g.*, WELCHOL®, COLESTID®, LoCholest and QUESTRAN®; and fibric acid derivatives, such as Atromid, LOPID® and Tricot); cholesterol ester transfer protein inhibitors (*e.g.*, torcetrapib and (2R)-3-{[3-(4-chloro-3-ethyl-phenoxy)-phenyl]-[[3-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]amino}-1,1,1-trifluoro-2-propanol); nicotinic acid and derivatives thereof (*e.g.*, niacin, acipimox); PCSK9 inhibitors; LXR agonists (*e.g.*, those disclosed in U.S. Patent Application Publication Nos. 2003/01814206, 2005/0080111, and 2005/0245515); lipoxygenase inhibitors (*e.g.*, such as benzimidazole derivatives, as disclosed in WO 97/12615, 15-LO inhibitors, as disclosed in WO 97/12613, isothiazolones, as disclosed in WO 96/38144, and 15-LO inhibitors, as disclosed by Sendobry et al., "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", *Brit. J. Pharmacology*, 120:1199-1206 (1997), and Cornicelli et al., "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", *Current Pharmaceutical Design*, 5:11-20 (1999)).

Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin, and rosuvastatin.

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 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 (*e.g.*, aliskiren), 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, vasopeptidase inhibitors (dual NEP-ACE inhibitors) (*e.g.*, omapatrilat and gemopatrilat), nitrates, central alpha agonists (*e.g.*, clonidine), alpha1 blockers (*e.g.*, prazosine), arterial vasodilators (*e.g.*, minoxidil), sympatolytics (*e.g.*, resperine), renin inhibitors (*e.g.*, Aliskiren (Novartis)).

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include a cannabinoid receptor 1 antagonist or inverse agonist (*e.g.*, rimonabant, (4S)-3-(4-chlorophenyl)-N-[(4-chlorophenyl)sulfonyl]-4,5-dihydro-N′-methyl-4-phenyl-1H-pyrazole-1-carboximidamide (SLV 319), CP-945598 (Pfizer), Surinabant (SR-147778, Sanofi-Aventis), N-[(1S,2S)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (Merck) and those discussed in Hertzog, D.L., *Expert Opin. Ther. Patents*, 14:1435-1452 (2004)); a beta 3 adrenergic agonist (*e.g.*, rafabegron (AJ9677, Takeda/Dainippon), N-[4-[2-[[(2S)-3-[(6-amino-3-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]phenyl]-4-(1-methylethyl)-benzenesulfonamide (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, with rafabegron, N-[4-[2-[[(2S)-3-[(6-amino-3-pyridinyl)oxy]-2-hydroxypropyl]amino]ethyl]phenyl]-4-(1-methylethyl)-benzenesulfonamide, and CP331648 being preferred); a lipase inhibitor (*e.g.*, orlistat or cetilistat, with orlistat being preferred); a serotonin and norepinephrine reuptake inhibitor (*e.g.*, sibutramine, Abbott and tesofensine, Neurosearch) with sibutramine being preferred; a dopamine reuptake inhibitor (*e.g.*, buproprion, GSK); or 5-HT_{2C} agonist, (*e.g.*, lorcaserin hydrochloride (Arena), WAY-163909 [(7bR,10aR)-1,2,3,4,8,9,10,10a-octahydro-7bH-cyclopenta-[b][1,4]diazepino[6,7,1hi]indole], with lorcaserin hydrochloride being preferred); 5-HT6 receptor antagonists (Suven, Biovitrum, Epix), anti-epileptics topiramate (Johnson & Johnson) and zonisamide, a ciliary neurotrophic factor agonist (*e.g.*, AXOKINE® (Regeneron); brain-derived neurotrophic factor (BDNF), orexin antagonists, histamine receptor-3 (H3)

modulators, melanin-concentrating hormone receptor (MCHR) antagonists (*e.g.*, GSK-856464 (GlaxoSmithKline), T-0910792 (Amgen)); diacylglycerol acyltransferase (DGAT) inhibitors (*e.g.*, BAY-74-4113 (Bayer),, PF-04620110, and LCQ908); acetyl- CoA carboxylase (ACC) inhibitors (*e.g.*, N-(4-(4-(4-isopropoxyphenoxy)phenyl)but-3-yn-2-yl)acetamide (A-80040, Abbott), (R)-anthracen-9-yl(3-(morpholine-4-carbonyl)-1,4′-bipiperidin-1′-yl)methanone (CP-640186, Pfizer)), SCD-1 inhibitors as described by Jiang et al., *Diabetes*, 53 (2004), (abs 653-p); amylin receptor agonists (*e.g.*, compounds disclosed in WO 2005/025504); thyroid receptor agonists (*e.g.*, as set forth above); growth hormone secretagogue receptor (GHSR) antagonists (*e.g.*, A-778193 (Abbott), leptin and leptin mimetics (*e.g.*, OB-3 (Aegis/Albany Medical College), leptin analogs A-100 and A-200 (Amgen), CBT-001452 (Cambridge Biotechnology), ML-22952 (Millennium)), PYY receptor agonist (*e.g.*, AC-162352 (Amylin), PYY-3-36 (Emishere), PYY(3-36)NH2 (Unigene)), NPY-Y4 agonists (7TM Pharma WO 2005/089786(A2,A3)-1), NPY-5 antagonists (*e.g.*, NPY5RA-972 (AstraZeneca), GW-594884A (GlaxoSmithKline), J-104870 (Banyu)); MTP/apoB secretion inhibitors (as set forth above), and/or an anorectic agent.

The anorectic agent which may be optionally employed in combination with compounds of the present invention include dexamphetamine, phentermine, phenylpropanolamine, or mazindol, with dexamphetamine being preferred.

Other compounds that can be used in combination with the compounds of the present invention include CCK receptor agonists (*e.g.*, SR-27895B); galanin receptor antagonists; MCR-4 antagonists (*e.g.*, N-acetyl-L-norleucyl-L-glutaminyl-L-histidyl-D-phenylalanyl-L-arginyl-D-tryptophyl-glycinamide, (HP-228); urocortin mimetics, CRF antagonists, and CRF binding proteins (*e.g.*, mifepristone (RU-486), urocortin).

Further, the compounds of the present invention may be used in combination with HIV protease inhibitors, including but not limited to REYATAZ® and KALETRA®.

Examples of suitable memory enhancing agents, anti-dementia agents, or cognition promoting agents for use in combination with the compounds of the present invention include, but are not limited to ARICEPT®, razadyne, donepezil,

rivastigmine, galantamine, memantine, tacrine, metrifonate, muscarine, xanomelline, deprenyl and physostigmine.

Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include, but are not limited to, NSAIDS, prednisone, acetaminophen, aspirin, codeine, fentanyl, ibuprofen, indomethacin, ketorolac, morphine, naproxen, phenacetin, piroxicam, sufentanyl, sunlindac, interferon alpha, prednisolone, methylprednisolone, dexamethazone, flucatisone, betamethasone, hydrocortisone, beclomethasone, REMICADE®, ORENCIA®, and ENBREL®.

The aforementioned patents and patent applications are incorporated herein by reference.

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*, as in the patents set out above, or as otherwise determined by one of ordinary skill in the art.

DOSAGE AND FORMULATION

The compounds of this disclosure can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the

effective amount of the drug required to prevent, counter, or arrest the progress of the disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, or between about 0.01 to 100 mg/kg of body weight per day, or alternatively, between about 1.0 to 20 mg/kg/day. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily. In one embodiment, the daily oral dosage of the active ingredient is between 3 and 600 mg either administered once daily or in divided doses administered twice daily. Alternatively, the active ingredient may be administered in doses of 10-20 mg administered twice daily or 40 to 100 mg administered once daily. Alternatively, the active ingredient may be administered a dose of 12.5 mg twice a day or 75 mg once a day. Alternatively, the active ingredient may be administered in doses of 3, 10, 30, 100, 300, and 600 mg administered either once or twice a day.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable

binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated

or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration may contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5

milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

Dispersion

A spray dried dispersion can be prepared for oral administration by methods known to one skilled in the art.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where two or more of the foregoing second therapeutic agents are administered with the compound of formula I, Ia, Ib, Ic, Id, Ie, If, Ig or II, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the examples and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to

minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

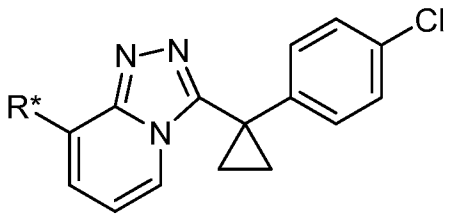
Additionally, certain compounds disclosed herein may be useful as metabolites of other compounds. Therefore, in one embodiment, compounds may be useful either as a substantially pure compound, which may also then be incorporated into a pharmaceutical composition, or may be useful as metabolite which is generated after administration of the prodrug of that compound. In one embodiment, a compound may be useful as a metabolite by being useful for treating disorders as described herein.

While it is apparent that the embodiments of the application herein disclosed are well suited to fulfill the objectives stated above, it will be appreciated that numerous modifications and other embodiments may be implemented by those skilled in the art, and it is intended that the appended claims cover all such modifications and embodiments that fall within the true spirit and scope of the present application.

A number of references have been cited and the entire disclosures of which are incorporated herein by reference.

WHAT IS CLAIMED IS:

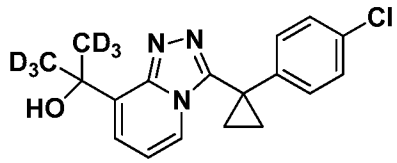
1. A compound, enantiomer, diastereomer, or salt thereof, of a compound of formula I:



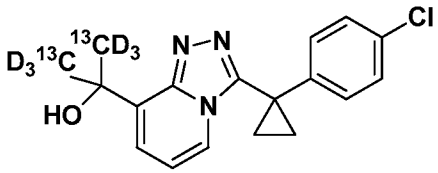
I

wherein R* is an isotopically labeled hydroxypropyl moiety.

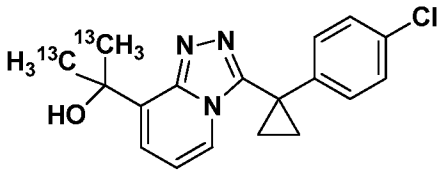
2. The compound, enantiomer, diastereomer, or salt thereof, of claim 1, wherein the compound is a compound of formula Ia, Ib, Ic, Id, Ie, If or Ig:



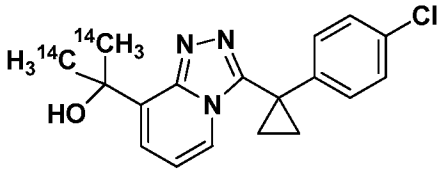
Ia ;



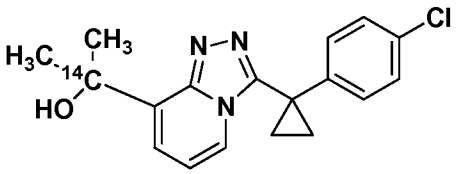
Ib ;



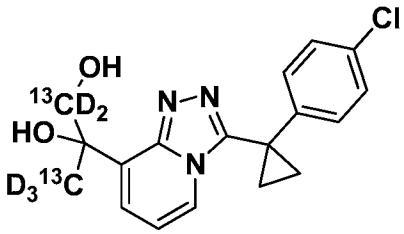
Ic ;



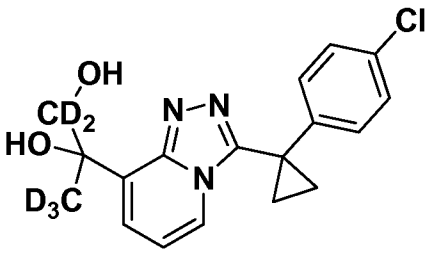
Id ;



Ie ;

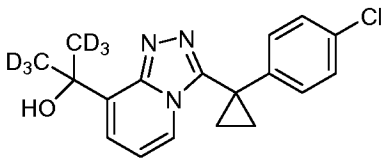


If ; or



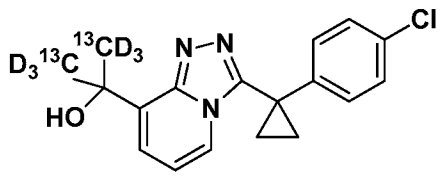
Ig.

3. The compound, enantiomer, diastereomer, or salt thereof, of claim 1, wherein the compound is a compound of formula Ia:



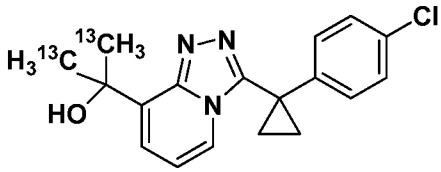
Ia.

4. The compound, enantiomer, diastereomer, or salt thereof, of claim 1, wherein the compound is a compound of formula Ib:



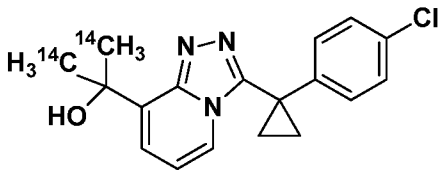
Ib.

5. The compound, enantiomer, diastereomer, or salt thereof, of claim 1, wherein the compound is a compound of formula Ic:



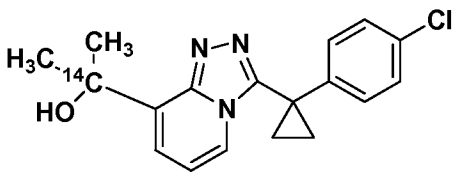
Ic.

6. The compound, enantiomer, diastereomer, or salt thereof, of claim 1, wherein the compound is a compound of formula Id:



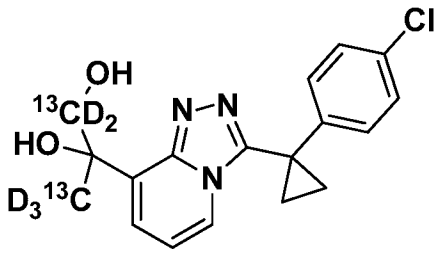
Id.

7. The compound, enantiomer, diastereomer, or salt thereof, of claim 1, wherein the compound is a compound of formula Ie:



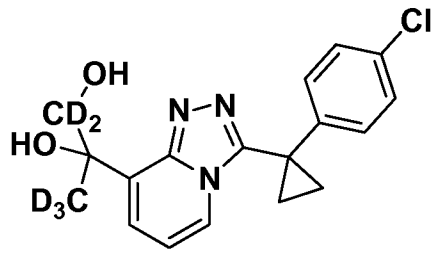
Ie.

8. A compound, enantiomer, diastereomer, or salt thereof, of a compound of formula If:



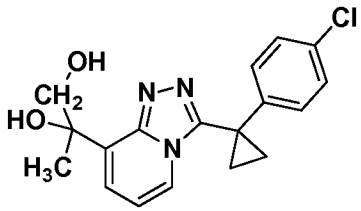
If.

9. A compound, enantiomer, diastereomer, or salt thereof, of a compound of formula Ig:



Ig.

10. A compound, enantiomer, diastereomer, or salt thereof, of a compound of formula II:



II.

11. A pharmaceutical composition comprising a compound of any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 10 further comprising at least one additional therapeutic agent.

13. A method for treating, preventing, or slowing the progression of diabetes, atherosclerosis, hyperglycemia, obesity, dyslipidemia, hypertension, cognitive impairment, rheumatoid arthritis, osteoarthritis, glaucoma, Cushing's Disease and Metabolic Syndrome, which comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of at least one compound, enantiomers, diastereomers, or salts thereof, of any one of claims 1 to 10.

14. A method for treating, preventing, or slowing the progression of diabetes, which comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of at least one compound, enantiomers, diastereomers, or salts thereof, of any one of claims 1 to 10.

15. A method for treating, preventing, or slowing the progression of atherosclerosis or dyslipidemia, which comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of at least one compound, enantiomers, diastereomers, or salts thereof, of any one of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/061509

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07B59/00 C07D471/04 A61K31/437 A61P3/10 A61P19/02
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07B C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/045753 A1 (BRISTOL-MYERS SQUIBB) 9 April 2009 (2009-04-09) cited in the application	10-15
Y	claim 14; examples 1, 4, 7, 9, 72, 82, 92	1,2,5-9, 11-15
A		3,4

Y	FOSTER A B: "Deuterium isotope effects in the metabolism of drugs and xenobiotics: implications for drug design", ADVANCES IN DRUG RESEARCH, ACADEMIC PRESS, LONDON, GB, vol. 14, 1985, pages 1-40, XP009086953, ISSN: 0065-2490 section 2	1,2,5-9, 11-15

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 December 2014	07/01/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	English, Russell

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/061509

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	R. TUNG: "The development of deuterium-containing drugs", INNOVATIONS IN PHARMACEUTICAL TECHNOLOGY, no. 32, March 2010 (2010-03), pages 24-26, 28, XP009148260, SAMEDAN LTD, GB ISSN: 1471-7204 paragraph bridging pages 24-25 -----	1,2,5-9, 11-15

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/061509

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/061509

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2009045753 A1	09-04-2009	AR 068601 A1	18-11-2009
		AU 2008309101 A1	09-04-2009
		CA 2701355 A1	09-04-2009
		CN 101883772 A	10-11-2010
		CO 6280485 A2	20-05-2011
		EA 201000563 A1	29-10-2010
		EA 201391705 A1	30-07-2014
		EP 2205598 A1	14-07-2010
		IL 204799 A	30-11-2014
		JP 2010540643 A	24-12-2010
		KR 20100085081 A	28-07-2010
		NZ 584386 A	30-03-2012
		PE 12192009 A1	14-08-2009
		PE 17042012 A1	17-12-2012
		SG 190638 A1	28-06-2013
		TW 200916470 A	16-04-2009
		US 2009093516 A1	09-04-2009
		US 2011288051 A1	24-11-2011
		WO 2009045753 A1	09-04-2009

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-15

Overall, the application concerns compounds of formula I and formula II and their use in treating, preventing or slowing the progression of the diseases listed in claims 13-15.

1.1. claims: 1-9(completely); 11-15(partially)

The first invention: compounds of formula I having an isotopically labeled hydroxypropyl group and their use in treating, preventing or slowing the progression of the diseases listed in claims 13-15.

1.2. claims: 10(completely); 11-15(partially)

The second invention: compounds of formula II and their use in treating, preventing or slowing the progression of the diseases listed in claims 13-15.
