Title: 3-FLUORO-BENZONITRILE INHIBITORS OF 11-BETA-HYDROXYLASE

Abstract: The present invention relates to new 3-fluoro-benzonitrile modulators of 11-β-hydroxylase, pharmaceutical compositions thereof, and methods of use thereof.

Formula I

[Continued on next page]
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3-FLUORO-BENZONITRILE INHIBITORS OF 11-β-HYDROXYLASE

This application claims the benefit of priority of United States provisional Application No. 62/098,722, filed December 31, 2014, the disclosure of which is hereby incorporated by reference, as if written herein, in its entirety.

[0001] Disclosed herein are new 3-fluoro-benzonitrile compounds and compositions and their application as pharmaceuticals for the treatment of disorders. Methods of inhibition of 11-β-hydroxylase activity in a subject are also provided for the treatment of disorders such as Cushing's disease, primary aldosteronism, hypertension, drug-resistant hypertension, essential hypertension, hypokalemia, hypertension, congestive heart failure, acute heart failure, heart failure, cachexia, acute coronary syndrome, chronic stress syndrome, Cushing's syndrome, metabolic syndrome, hypercortisolemia, atrial fibrillation, renal failure, chronic renal failure, restenosis, sleep apnea, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart disease, increased formation of collagen, cardiac or myocardial fibrosis and/or remodeling following hypertension and endothelial dysfunction, Conn's disease, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, arrhythmia, diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertrophic cardiomyopathy, sudden cardiac death, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, fibrinoid, necrosis of coronary arteries, ectopic ACTH syndrome, change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD), Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine withdrawal syndrome, cocaine withdrawal syndrome, post-traumatic stress syndrome, cognitive impairment after a stroke or cortisol-induced mineral corticoid excess, ventricular arrhythmia, estrogen-dependent disorders, gynecomastia, osteoporosis, prostate cancer, endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycystic ovarian disease, infertility, fibrocystic breast disease, breast cancer, and fibrocystic mastopathy.

[0002] Osilodrostat (LCI699; 4-[(5R)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl]-3-fluoro-benzonitrile; CAS# 928134-65-0). Osilodrostat is a 11-β-hydroxylase inhibitor.
Osilodrostat is currently under investigation for the treatment of Cushing's disease, primary aldosteronism, and hypertension. Osilodrostat has also shown promise in treating drug-resistant hypertension, essential hypertension, hypokalemia, hypertension, congestive heart failure, acute heart failure, heart failure, cachexia, acute coronary syndrome, chronic stress syndrome, Cushing's syndrome, metabolic syndrome, hypercortisolism, atrial fibrillation, renal failure, chronic renal failure, restenosis, sleep apnea, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heavy disease, increased formation of collagen, cardiac or myocardial fibrosis and/or remodeling following hypertension and endothelial dysfunction, Conn's disease, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, arrhythmia, diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertrophic cardiomyopathy, sudden cardiac death, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, fibrinoid, necrosis of coronary arteries, ectopic ACTH syndrome, change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD), Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine withdrawal syndrome, cocaine withdrawal syndrome, post-traumatic stress syndrome, cognitive impairment after a stroke or cortisol-induced mineral corticoid excess, ventricular arrhythmia, estrogen-dependent disorders, gynecomastia, osteoporosis, prostate cancer, endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycystic ovarian disease, infertility, fibrocystic breast disease, breast cancer, and fibrocystic mastopathy. WO 2013 109514; WO 2007024945; and WO 201 1064376.

Osilodrostat is likely subject to extensive CYP450-mediated oxidative metabolism. These, as well as other metabolic transformations, occur in part through polymorphically-expressed enzymes, exacerbating interpatient variability. Additionally, some metabolites of
osilodrostat derivatives may have undesirable side effects. In order to overcome its short half-life, the drug likely must be taken several times per day, which increases the probability of patient incompliance and discontinuance. Adverse effects associated with osilodrostat include fatigue, nausea, diarrhea, headache, hypokalemia, muscle spasms, vomiting, abdominal discomfort, abdominal pain, arthralgia, arthropod bite, dizziness, increased lipase, and pruritis.

**Deuterium Kinetic Isotope Effect**

[0004] In order to eliminate foreign substances such as therapeutic agents, the animal body expresses various enzymes, such as the cytochrome P450 enzymes (CYPs), esterases, proteases, reductases, dehydrogenases, and monoamine oxidases, to react with and convert these foreign substances to more polar intermediates or metabolites for renal excretion. Such metabolic reactions frequently involve the oxidation of a carbon-hydrogen (C-H) bond to either a carbon-oxygen (C-O) or a carbon-carbon (C-C) π-bond. The resultant metabolites may be stable or unstable under physiological conditions, and can have substantially different pharmacokinetic, pharmacodynamic, and acute and long-term toxicity profiles relative to the parent compounds. For most drugs, such oxidations are generally rapid and ultimately lead to administration of multiple or high daily doses.

[0005] The relationship between the activation energy and the rate of reaction may be quantified by the Arrhenius equation, \( k = A e^{-E_{act}/RT} \). The Arrhenius equation states that, at a given temperature, the rate of a chemical reaction depends exponentially on the activation energy \( (E_{act}) \).

[0006] The transition state in a reaction is a short lived state along the reaction pathway during which the original bonds have stretched to their limit. By definition, the activation energy \( E_{act} \) for a reaction is the energy required to reach the transition state of that reaction. Once the transition state is reached, the molecules can either revert to the original reactants, or form new bonds giving rise to reaction products. A catalyst facilitates a reaction process by lowering the activation energy leading to a transition state. Enzymes are examples of biological catalysts.

[0007] Carbon-hydrogen bond strength is directly proportional to the absolute value of the ground-state vibrational energy of the bond. This vibrational energy depends on the mass of the atoms that form the bond, and increases as the mass of one or both of the atoms making the bond increases. Since deuterium (D) has twice the mass of protium (\( \frac{3}{4} \)), a C-D bond is
stronger than the corresponding C-¾ bond. If a C-¾ bond is broken during a rate-
determining step in a chemical reaction (i.e. the step with the highest transition state energy),
then substituting a deuterium for that protium will cause a decrease in the reaction rate. This
phenomenon is known as the Deuterium Kinetic Isotope Effect (DKIE). The magnitude of the
DKIE can be expressed as the ratio between the rates of a given reaction in which a C-¾
bond is broken, and the same reaction where deuterium is substituted for protium. The DKIE
can range from about 1 (no isotope effect) to very large numbers, such as 50 or more.
Substitution of tritium for hydrogen results in yet a stronger bond than deuterium and gives
numerically larger isotope effects.

Deuterium (²H or D) is a stable and non-radioactive isotope of hydrogen which has approximately
twice the mass of protium (¹H), the most common isotope of hydrogen. Deuterium oxide (D₂O or "heavy water") looks and tastes like H₂O, but has different physical properties.

When pure D₂O is given to rodents, it is readily absorbed. The quantity of
deuterium required to induce toxicity is extremely high. When about 0-1.5% of the body
water has been replaced by D₂O, animals are healthy but are unable to gain weight as fast as
the control (untreated) group. When about 15-20% of the body water has been replaced with
D₂O, the animals become excitable. When about 20-25% of the body water has been
replaced with D₂O, the animals become so excitable that they go into frequent convulsions
when stimulated. Skin lesions, ulcers on the paws and muzzles, and necrosis of the tails
appear. The animals also become very aggressive. When about 30% of the body water has
been replaced with D₂O, the animals refuse to eat and become comatose. Their body weight
drops sharply and their metabolic rates drop far below normal, with death occurring at about
30 to about 35% replacement with D₂O. The effects are reversible unless more than thirty
percent of the previous body weight has been lost due to D₂O. Studies have also shown that
the use of D₂O can delay the growth of cancer cells and enhance the cytotoxicity of certain
antineoplastic agents.

Deuteration of pharmaceuticals to improve pharmacokinetics (PK),
pharmacodynamics (PD), and toxicity profiles has been demonstrated previously with some
classes of drugs. For example, the DKIE was used to decrease the hepatotoxicity of
halothane, presumably by limiting the production of reactive species such as trifluoroacetyl chloride. However, this method may not be applicable to all drug classes. For example,
deuterium incorporation can lead to metabolic switching. Metabolic switching occurs when
xenogens, sequestered by Phase I enzymes, bind transiently and re-bind in a variety of
conformations prior to the chemical reaction (e.g., oxidation). Metabolic switching is enabled by the relatively vast size of binding pockets in many Phase I enzymes and the promiscuous nature of many metabolic reactions. Metabolic switching can lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity. Such pitfalls are non-obvious and are not predictable apriori for any drug class.

[0011] Osilodrostat is a 11-β-hydroxylase inhibitor. The carbon-hydrogen bonds of osilodrostat contain a naturally occurring distribution of hydrogen isotopes, namely ¾ or protium (about 99.9844%), ²H or deuterium (about 0.0156%), and ¾ or tritium (in the range between about 0.5 and 67 tritium atoms per 10¹⁸ protium atoms). Increased levels of deuterium incorporation may produce a detectable Deuterium Kinetic Isotope Effect (DKIE) that could affect the pharmacokinetic, pharmacologic and/or toxicologic profiles of such osilodrostat in comparison with the compound having naturally occurring levels of deuterium.

[0012] Based on discoveries made in our laboratory, as well as considering the literature, osilodrostat is likely metabolized in humans at the 2- and 4-positions of the imidazole ring, the fused pyrrolodine ring, and the phenyl ring. The current approach has the potential to prevent metabolism at these sites. Other sites on the molecule may also undergo transformations leading to metabolites with as-yet-unknown pharmacology/toxicology. Limiting the production of these metabolites has the potential to decrease the danger of the administration of such drugs and may even allow increased dosage and/or increased efficacy. All of these transformations can occur through polymorphically-expressed enzymes, exacerbating interpatient variability. Further, some disorders are best treated when the subject is medicated around the clock or for an extended period of time. For all of the foregoing reasons, a medicine with a longer half-life may result in greater efficacy and cost savings. Various deuteration patterns can be used to (a) reduce or eliminate unwanted metabolites, (b) increase the half-life of the parent drug, (c) decrease the number of doses needed to achieve a desired effect, (d) decrease the amount of a dose needed to achieve a desired effect, (e) increase the formation of active metabolites, if any are formed, (f) decrease the production of deleterious metabolites in specific tissues, and/or (g) create a more effective drug and/or a safer drug for polypharmacy, whether the polypharmacy be intentional or not. The deuteration approach has the strong potential to slow the metabolism of osilodrostat and attenuate interpatient variability.
Novel compounds and pharmaceutical compositions, certain of which have been found to inhibit 11-β-hydroxylase have been discovered, together with methods of synthesizing and using the compounds, including methods for the treatment of 11-β-hydroxylase-mediated disorders in a patient by administering the compounds.

Accordingly, provided herein are compounds of structural Formula I:

![Structural Formula I](image)

or a salt thereof, wherein:

**Ri-Rio** are independently chosen from hydrogen and deuterium; and

at least one of **Ri-Rio** is deuterium or contains deuterium.

Accordingly, also provided herein are enantiomers of compounds of Formula I, designated Formulas 1a and 1b:

![Enantiomers 1a and 1b](image)

Accordingly, also provided herein are compounds of structural Formula 1a:
or a salt thereof, wherein:

Ri-Rio are independently chosen from hydrogen and deuterium; and

at least one of Ri-Rio is deuterium or contains deuterium.

[0017] In certain embodiments, Ri is deuterium.
[0018] In certain embodiments, R7 is deuterium.
[0019] In certain embodiments, Ri and R7 are deuterium.
[0020] In certain embodiments, R3 and R4 are deuterium.
[0021] In certain embodiments, R5 and R6 are deuterium.
[0022] In certain embodiments, R3-R6 are deuterium.
[0023] In certain embodiments, Ri and R3-R6 are deuterium.
[0024] In certain embodiments, R7 and R3-R6 are deuterium.
[0025] In certain embodiments, Ri, R7, and R3-R6 are deuterium.
[0026] Also provided herein are embodiments according to each of the embodiments above, wherein every other substituent among R1-R10 not specified as deuterium is hydrogen.
[0027] In certain embodiments are provided compounds as disclosed herein, wherein at least one of R1-R10 independently has deuterium enrichment of no less than about 1%. In certain embodiments are provided compounds as disclosed herein, wherein at least one of R1-R10 independently has deuterium enrichment of no less than about 10%. In certain embodiments are provided compounds as disclosed herein, wherein at least one of R1-R10 independently has deuterium enrichment of no less than about 50%. In certain embodiments are provided compounds as disclosed herein, wherein at least one of R1-R10 independently has deuterium enrichment of no less than about 90%.
enrichment of no less than about 95%. In certain embodiments are provided compounds as disclosed herein, wherein at least one of R1-R10 independently has deuterium enrichment of no less than about 98%.

[0028] The compounds as disclosed herein may also contain less prevalent isotopes for other elements, including, but not limited to, $^{13}$C or $^{14}$C for carbon, $^{33}$S, $^{34}$S, or $^{36}$S for sulfur, $^{15}$N for nitrogen, and $^{17}$O or $^{18}$O for oxygen.

[0029] In certain embodiments, the compound disclosed herein may expose a patient to a maximum of about 0.000005% D$_2$O or about 0.00001% DHO, assuming that all of the C-D bonds in the compound as disclosed herein are metabolized and released as D$_2$O or DHO. In certain embodiments, the levels of D$_2$O shown to cause toxicity in animals is much greater than even the maximum limit of exposure caused by administration of the deuterium enriched compound as disclosed herein. Thus, in certain embodiments, the deuterium-enriched compound disclosed herein should not cause any additional toxicity due to the formation of D$_2$O or DHO upon drug metabolism.

[0030] Also provided is a compound chosen from the Examples and compounds disclosed herein.

[0031] In certain embodiments are provided compounds as disclosed herein, wherein each position represented as D has deuterium enrichment of no less than about 1%. In certain embodiments are provided compounds as disclosed herein, wherein each position represented as D has deuterium enrichment of no less than about 10%. In certain embodiments are provided compounds as disclosed herein, wherein each position represented as D has deuterium enrichment of no less than about 50%. In certain embodiments are provided compounds as disclosed herein, wherein each position represented as D has deuterium enrichment of no less than about 90%. In certain embodiments are provided compounds as disclosed herein, wherein each position represented as D has deuterium enrichment of no less than about 95%. In certain embodiments are provided compounds as disclosed herein, wherein each position represented as D has deuterium enrichment of no less than about 98%.

[0032] In certain embodiments, the deuterated compounds disclosed herein maintain the beneficial aspects of the corresponding non-isotopically enriched molecules while substantially increasing the maximum tolerated dose, decreasing toxicity, increasing the half-life (T1/2), lowering the maximum plasma concentration (C$_{max}$) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.
[0033] All publications and references cited herein are expressly incorporated herein by reference in their entirety. However, with respect to any similar or identical terms found in both the incorporated publications or references and those explicitly put forth or defined in this document, then those terms definitions or meanings explicitly put forth in this document shall control in all respects.

[0034] Certain compounds disclosed herein may possess useful 11-β-hydroxylase inhibiting activity, and may be used in the treatment or prophylaxis of a disorder in which 11-β-hydroxylase plays an active role. Thus, certain embodiments also provide pharmaceutical compositions comprising one or more compounds disclosed herein together with a pharmaceutically acceptable carrier, as well as methods of making and using the compounds and compositions. Certain embodiments provide methods for inhibiting 11-β-hydroxylase. Other embodiments provide methods for treating a 11-β-hydroxylase-mediated disorder in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a compound or composition according to the present invention. Also provided is the use of certain compounds disclosed herein for use in the manufacture of a medicament for the prevention or treatment of a disorder ameliorated by the inhibition of 11-β-hydroxylase.

[0035] Also provided is a method of treatment of an 11-β-hydroxylase-mediated disorder comprising the administration of a therapeutically effective amount of a compound, or a salt thereof, as disclosed herein to a patient in need thereof.

[0036] In certain embodiments, the disorder is chosen from Cushing's disease, primary aldosteronism, hypertension, drug-resistant hypertension, essential hypertension, hypokalemia, hypertension, congestive heart failure, acute heart failure, heart failure, cachexia, acute coronary syndrome, chronic stress syndrome, Cushing's syndrome, metabolic syndrome, hypercortisolemia, atrial fibrillation, renal failure, chronic renal failure, restenosis, sleep apnea, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart disease, increased formation of collagen, cardiac or myocardial fibrosis and/or remodeling following hypertension and endothelial dysfunction, Conn's disease, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, arrhythmia, diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertrophic cardiomyopathy, sudden cardiac death, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased
ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, fibrinoid, necrosis of coronary arteries, ectopic ACTH syndrome, change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD), Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine withdrawal syndrome, cocaine withdrawal syndrome, post-traumatic stress syndrome, cognitive impairment after a stroke or cortisol-induced mineral corticoid excess, ventricular arrhythmia, estrogen-dependent disorders, gynecomastia, osteoporosis, prostate cancer, endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycystic ovarian disease, infertility, fibrocystic breast disease, breast cancer, and fibrocystic mastopathy.

[0037] In certain embodiments, the method of treatment further comprises the administration of an additional therapeutic agent.

[0038] In certain embodiments, the additional therapeutic agent is chosen from adrenergic receptor antagonists, angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, anti-arrhythmics, anticoagulants, antiplatelet agents, beta-1 adrenergic receptor antagonists, calcium channel blockers, fibrates, platelet aggregation inhibitors, HMG-CoA reductase inhibitors, and diuretics.

[0039] In certain embodiments, the adrenergic receptor antagonist is chosen from atenolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, timolol, doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, tolazoline, bucindolol, carvedilol, and labetalol.

[0040] In certain embodiments, the angiotensin II receptor antagonist is chosen from candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, valsartan, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, molsidomin, and pentaerythritol tetranitrate.

[0041] In certain embodiments, the angiotensin-converting enzyme inhibitor is chosen from captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, benazepril, cilazapril, fosinopril, trandolapril, spirapril, delapril, moexipril, temocapril, zofenopril, and imidapril.

[0042] In certain embodiments, the anti-arrhythmic is chosen from quinidine, procainamide, disopyramide, sparteine, ajmaline, prajmaline, lorajmine, lidocaine, mexiletine, tocainide, aprindine, propafenone, flecaïnide, lorcaïnide, encainide, amiodarone, bretylium tosilate, bunaftine, dofetilide, ibutilidem, moracizine, and cibenzoline.

[0043] In certain embodiments, the anticoagulant is chosen from acenocoumarol, argatroban, bivalirudin, lepirudin, fondaparinux, heparin, phenindione, warfarin, and ximelagatran.
In certain embodiments, the antiplatelet agent is chosen from abciximab, cilostazol, clopidogrel, dipyridamole, ticlopidine, and tirofibin.

In certain embodiments, the beta-1 adrenergic receptor antagonist is chosen from betaxolol, alprenolol, oxprenolol, pindolol, propranolol, timolol, sotalol, nadolol, mepindolol, carteolol, tertatolol, bopindolol, upranolol, penbutolol, cloranolol, practolol, metoprolol, atenolol, acebutolol, bevantolol, bisoprolol, celiprolol, esmolol, epanolol, s-atenolol, nebivolol, talinolol, labetalol, and carvedilol.

In certain embodiments, the calcium channel blocker is chosen from amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, nilvadipine, manidipine, barnidipine, lercanidipine, cilnidipine, bendidipine, mibebradil, verapamil, gallopamil, diltiazem, fendiline, bepridil, lidoflazine, and perhexiline.

In certain embodiments, the fibrate is chosen from clofibrate, bezafibrate, aluminum clofibrate, gemfibrozil, fenofibrate, simfibrate, ronifibrate, ciprofibrate, etofibrate, and clofibride.

In certain embodiments, the platelet aggregation inhibitor is chosen from acetylsalicylic acid/aspirin, aloxiprin, ditazole, carbasalate calcium, cloricromen, dipyridamole, indobufen, picotamide, triflusal, clopidogrel, ticlopidine, prasugrel, beraprost, prostacyclin, iloprost, and treprostinil.

In certain embodiments, the HMG-CoA reductase inhibitor is chosen from atorvastatin, cerivastatin, fluuvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

In certain embodiments, the diuretic is chosen from bendroflumethiazide, hydroflumethiazide, hydrochlorothiazide, chlorothiazide, polythiazide, trichlormethiazide, cyclopenthiazide, methyclothiazide, cyclothiazide, mebutizide, quinethazone, clopamide, chlortaldione, mefruside, clofenamide, metolazone, meticrane, xipamide, indapamide, clorexlolone, fenquizone, mersaly1, theobromine, cicloctane, furosemide, bumetanide, piretanide, torasemide, etacrynlic acid, tienilic acid, muzolimine, etozolin, spironolactone, potassium canrenoate, canrenone, and eplerenone.

In certain embodiments, the method of treatment further results in at least one effect chosen from:

a) decreased inter-individual variation in plasma levels of the compound or a metabolite thereof as compared to the non-isotopically enriched compound;

b) increased average plasma levels of the compound per dosage unit thereof as compared to the non-isotopically enriched compound;
c) decreased average plasma levels of at least one metabolite of the compound per dosage unit thereof as compared to the non-isotopically enriched compound;
d) increased average plasma levels of at least one metabolite of the compound per dosage unit thereof as compared to the non-isotopically enriched compound; and
e) an improved clinical effect during the treatment in the subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0052] In certain embodiments, the method of treatment further results in at least two effects chosen from:
a) decreased inter-individual variation in plasma levels of the compound or a metabolite thereof as compared to the non-isotopically enriched compound;
b) increased average plasma levels of the compound per dosage unit thereof as compared to the non-isotopically enriched compound;
c) decreased average plasma levels of at least one metabolite of the compound per dosage unit thereof as compared to the non-isotopically enriched compound;
d) increased average plasma levels of at least one metabolite of the compound per dosage unit thereof as compared to the non-isotopically enriched compound; and
e) an improved clinical effect during the treatment in the subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0053] In certain embodiments, the method effects a decreased metabolism of the compound per dosage unit thereof by at least one polymorphically-expressed cytochrome P<sub>450</sub> isoform in the subject, as compared to the corresponding non-isotopically enriched compound.

[0054] In certain embodiments, the cytochrome P<sub>450</sub> isoform is chosen from CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[0055] In certain embodiments, the compound is characterized by decreased inhibition of at least one cytochrome P<sub>450</sub> or monoamine oxidase isoform in the subject per dosage unit thereof as compared to the non-isotopically enriched compound.

[0056] In certain embodiments, the cytochrome P<sub>450</sub> or monoamine oxidase isoform is chosen from CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1,
CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP51, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, MAO A, and MAOB.

[0057] In certain embodiments, the method reduces a deleterious change in a diagnostic hepatobiliary function endpoint, as compared to the corresponding non-isotopically enriched compound.

[0058] In certain embodiments, the diagnostic hepatobiliary function endpoint is chosen from alanine aminotransferase ("ALT"), serum glutamic-pyruvic transaminase ("SGPT"), aspartate aminotransferase ("AST," "SGOT"), ALT/AST ratios, serum aldolase, alkaline phosphatase ("ALP"), ammonia levels, bilirubin, gamma-glutamyl transpeptidase ("GGTP," "γ-GTP," "GGT"), leucine aminopeptidase ("LAP"), liver biopsy, liver ultrasonography, liver nuclear scan, 5'-nucleotidase, and blood protein.

[0059] Also provided is a compound as disclosed herein for use as a medicament.

[0060] Also provided is a compound as disclosed herein for use in the manufacture of a medicament for the prevention or treatment of a disorder ameliorated by the inhibition of 11-β-hydroxylase.

[0061] As used herein, the terms below have the meanings indicated.

[0062] The singular forms "a," "an," and "the" may refer to plural articles unless specifically stated otherwise.

[0063] The term "about," as used herein, is intended to qualify the numerical values which it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term "about" should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[0064] When ranges of values are disclosed, and the notation "from m₁ ... to m₂" or "m-₁ to m₂" is used, where m and n₂ are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values.

[0065] The term "deuterium enrichment" refers to the percentage of incorporation of deuterium at a given position in a molecule in the place of hydrogen. For example, deuterium enrichment of 1% at a given position means that 1% of molecules in a given sample contain deuterium at the specified position. Because the naturally occurring distribution of deuterium...
is about 0.0156%, deuterium enrichment at any position in a compound synthesized using non-enriched starting materials is about 0.0156%. The deuterium enrichment can be determined using conventional analytical methods known to one of ordinary skill in the art, including mass spectrometry and nuclear magnetic resonance spectroscopy.

[0066] The term "is/are deuterium," when used to describe a given position in a molecule such as Ri-Rio or the symbol "D", when used to represent a given position in a drawing of a molecular structure, means that the specified position is enriched with deuterium above the naturally occurring distribution of deuterium. In one embodiment deuterium enrichment is no less than about 1%, in another no less than about 5%, in another no less than about 10%, in another no less than about 20%, in another no less than about 50%, in another no less than about 70%, in another no less than about 80%, in another no less than about 90%, or in another no less than about 98% of deuterium at the specified position.

[0067] The term "isotopic enrichment" refers to the percentage of incorporation of a less prevalent isotope of an element at a given position in a molecule in the place of the more prevalent isotope of the element.

[0068] The term "non-isotopically enriched" refers to a molecule in which the percentages of the various isotopes are substantially the same as the naturally occurring percentages.

[0069] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols "R" or "S," depending on the configuration of substituents around the chiral carbon atom. It should be understood that the invention encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and l-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques known in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this invention. Additionally, the compounds disclosed herein can exist in unsolvated as well as
solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[0070] The term "bond" refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[0071] The term "disorder" as used herein is intended to be generally synonymous, and is used interchangeably with, the terms "disease" and "condition" (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms.

[0072] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder or one or more of the symptoms associated with a disorder; or alleviating or eradicating the cause(s) of the disorder itself. As used herein, reference to "treatment" of a disorder is intended to include prevention. The terms "prevent," "preventing," and "prevention" refer to a method of delaying or precluding the onset of a disorder; and/or its attendant symptoms, barring a subject from acquiring a disorder or reducing a subject's risk of acquiring a disorder.

[0073] The term "therapeutically effective amount" refers to the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0074] The term "subject" refers to an animal, including, but not limited to, a primate (e.g., human, monkey, chimpanzee, gorilla, and the like), rodents (e.g., rats, mice, gerbils, hamsters, ferrets, and the like), lagomorphs, swine (e.g., pig, miniature pig), equine, canine, feline, and the like. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human patient.

[0075] The term "combination therapy" means the administration of two or more therapeutic agents to treat a therapeutic disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also
encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the disorders described herein.

[0076] The term "11-β-hydroxylase" refers to an enzyme of the cytochrome P450 superfamily (CYP1 IB1) found in the zona glomerulosa and zona fasciculata. 11-β-hydroxylase localizes to the mitochondrial inner membrane and is involved in the conversion of 11-deoxyCortisol to Cortisol in the adrenal cortex.

[0077] The term "11-β-hydroxylase-mediated disorder," refers to a disorder that is characterized by abnormal 11-β-hydroxylase activity. A 11-β-hydroxylase-mediated disorder may be completely or partially mediated by modulating 11-β-hydroxylase activity. In particular, a 11-β-hydroxylase-mediated disorder is one in which inhibition of 11-β-hydroxylase results in some effect on the underlying disorder e.g., administration of a 11-β-hydroxylase inhibitor results in some improvement in at least some of the patients being treated.

[0078] The term "11-β-hydroxylase inhibitor," refers to the ability of a compound disclosed herein to alter the function of 11-β-hydroxylase. An inhibitor may block or reduce the activity of 11-β-hydroxylase by forming a reversible or irreversible covalent bond between the inhibitor and 11-β-hydroxylase or through formation of a noncovalently bound complex. Such inhibition may be manifest only in particular cell types or may be contingent on a particular biological event. The term "inhibit" or "inhibition" also refers to altering the function of 11-β-hydroxylase by decreasing the probability that a complex forms between 11-β-hydroxylase and a natural substrate. In some embodiments, inhibition of 11-β-hydroxylase may be assessed using the methods described in WO 201 1064376 and WO 2007024945.

[0079] The term "therapeutically acceptable" refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without excessive toxicity, irritation, allergic response, immunogenicity, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0080] The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. Each component must be "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation. It must also be suitable for use in contact with the tissue or
organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenecity, or other problems or complications, commensurate with a reasonable benefit/risk ratio.

[0081] The terms "active ingredient," "active compound," and "active substance" refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients or carriers, to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder.

[0082] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a disorder.

[0083] The term "release controlling excipient" refers to an excipient whose primary function is to modify the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0084] The term "nonrelease controlling excipient" refers to an excipient whose primary function do not include modifying the duration or place of release of the active substance from a dosage form as compared with a conventional immediate release dosage form.

[0085] The term "prodrug" refers to a compound functional derivative of the compound as disclosed herein and is readily convertible into the parent compound in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms, including enzymatic processes and metabolic hydrolysis.

[0086] The compounds disclosed herein can exist as therapeutically acceptable salts. The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound with a suitable acid or base.

Therapeutically acceptable salts include acid and basic addition salts.

[0087] Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1 S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid,
cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, a-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (±)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, or sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic and aromatic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, N-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

While it may be possible for the compounds of the subject invention to be administered as the raw chemical, it is also possible to present them as a pharmaceutical composition. Accordingly, provided herein are pharmaceutical compositions which comprise one or more of certain compounds disclosed herein, or one or more pharmaceutically acceptable salts, prodrugs, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art, e.g., in Remington's Pharmaceutical Sciences. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes. The pharmaceutical compositions may also be formulated as a
modified release dosage form, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art.

[0090] The compositions include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound of the subject invention or a pharmaceutically salt, prodrug, or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0091] Formulations of the compounds disclosed herein suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

[0092] Pharmaceutical preparations which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants
such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[0093] The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[0094] Formulations for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0095] In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or
hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange
resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0096] For buccal or sublingual administration, the compositions may take the form of
tables, lozenges, pastilles, or gels formulated in conventional manner. Such compositions
may comprise the active ingredient in a flavored basis such as sucrose and acacia or
tragacanth.

[0097] The compounds may also be formulated in rectal compositions such as
suppositories or retention enemas, e.g., containing conventional suppository bases such as
cocoa butter, polyethylene glycol, or other glycerides.

[0098] Certain compounds disclosed herein may be administered topically, that is by non-
 systemic administration. This includes the application of a compound disclosed herein
externally to the epidermis or the buccal cavity and the instillation of such a compound into
the ear, eye and nose, such that the compound does not significantly enter the blood stream.
In contrast, systemic administration refers to oral, intravenous, intraperitoneal and
intramuscular administration.

[0099] Formulations suitable for topical administration include liquid or semi-liquid
preparations suitable for penetration through the skin to the site of inflammation such as gels,
liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the
eye, ear or nose.

[00100] For administration by inhalation, compounds may be delivered from an
insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol
spray. Pressurized packs may comprise a suitable propellant such as
dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide
or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined
by providing a valve to deliver a metered amount. Alternatively, for administration by
inhalation or insufflation, the compounds according to the invention may take the form of a
dry powder composition, for example a powder mix of the compound and a suitable powder
base such as lactose or starch. The powder composition may be presented in unit dosage
form, in for example, capsules, cartridges, gelatin or blister packs from which the powder
may be administered with the aid of an inhalator or insufflator.

[00101] Preferred unit dosage formulations are those containing an effective dose, as
herein below recited, or an appropriate fraction thereof, of the active ingredient.

[00102] Compounds may be administered orally or via injection at a dose of from 0.1 to
500 mg/kg per day. The dose range for adult humans is generally from 5 mg to 2 g/day.
Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of one or more compounds which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg.

[00103] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

[00104] The compounds can be administered in various modes, e.g. orally, topically, or by injection. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the disorder being treated. Also, the route of administration may vary depending on the disorder and its severity.

[00105] In the case wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds may be administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disorder.

[00106] In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds may be given continuously or temporarily suspended for a certain length of time (i.e., a "drug holiday").

[00107] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, can be reduced, as a function of the symptoms, to a level at which the improved disorder is retained. Patients can, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00108] Disclosed herein are methods of treating a 11-β-hydroxylase-mediated disorder comprising administering to a subject having or suspected to have such a disorder, a therapeutically effective amount of a compound as disclosed herein or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00109] 11-β-Hydroxylase-mediated disorders, include, but are not limited to, Cushing's disease, primary aldosteronism, hypertension, drug-resistant hypertension, essential hypertension, hypokalemia, hypertension, congestive heart failure, acute heart failure, heart failure, cachexia, acute coronary syndrome, chronic stress syndrome, Cushing's syndrome,
metabolic syndrome, hypercortisolemia, atrial fibrillation, renal failure, chronic renal failure, restenosis, sleep apnea, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary hea ry disease, increased formation of collagen, cardiac or myocardial fibrosis and/or remodeling following hypertension and endothelial dysfunction, Conn's disease, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, arrhythmia, diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertrophic cardiomyopathy, sudden cardia death, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, fibrinoid, necrosis of coronary arteries, ectopic ACTH syndrome, change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD), Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine withdrawal syndrome, cocaine withdrawal syndrome, post-traumatic stress syndrome, cognitive impairment after a stroke or cortisol-induced mineral corticoid excess, ventricular arrhythmia, estrogen-dependent disorders, gynecomastia, osteoporosis, prostate cancer, endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycystic ovarian disease, infertility, fibrocystic breast disease, breast cancer, and fibrocystic mastopathy, and/or any disorder which can lessened, alleviated, or prevented by administering a 11-β-hydroxylase inhibitor.

[001 10] In certain embodiments, a method of treating a 11-β-hydroxylase-mediated disorder comprises administering to the subject a therapeutically effective amount of a compound of as disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, so as to affect: (1) decreased inter-individual variation in plasma levels of the compound or a metabolite thereof; (2) increased average plasma levels of the compound or decreased average plasma levels of at least one metabolite of the compound per dosage unit; (3) decreased inhibition of, and/or metabolism by at least one cytochrome P450 or monoamine oxidase isoform in the subject; (4) decreased metabolism via at least one polymorphically-expressed cytochrome P450 isoform in the subject; (5) at least one statistically-significantly improved disorder-control and/or disorder-eradication endpoint; (6) an improved clinical effect during the treatment of the disorder, (7) prevention of recurrence, or delay of decline or appearance, of abnormal alimentary or hepatic parameters as the primary clinical benefit, or
(8) reduction or elimination of deleterious changes in any diagnostic hepatobiliary function endpoints, as compared to the corresponding non-isotopically enriched compound.

[0011] In certain embodiments, inter-individual variation in plasma levels of the compounds as disclosed herein, or metabolites thereof, is decreased; average plasma levels of the compound as disclosed herein are increased; average plasma levels of a metabolite of the compound as disclosed herein are decreased; inhibition of a cytochrome \( p_{450} \) or monoamine oxidase isoform by a compound as disclosed herein is decreased; or metabolism of the compound as disclosed herein by at least one polymorphically-expressed cytochrome \( p_{450} \) isoform is decreased; by greater than about 5%, greater than about 10%, greater than about 20%, greater than about 30%, greater than about 40%, or by greater than about 50% as compared to the corresponding non-isotopically enriched compound.

[0012] Examples of cytochrome \( p_{450} \) isoforms in a mammalian subject include, but are not limited to, CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2D1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7B1, CYP8A1, CYP8B1, CYP1A1, CYP1B1, CYP1B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, and CYP51.

[0013] Examples of monoamine oxidase isoforms in a mammalian subject include, but are not limited to, MAOA, and MAOB.

[0014] The inhibition of the cytochrome \( p_{450} \) isoform is measured by the method of Ko et al. \((British Journal of Clinical Pharmacology, 2000, 49, 343-351)\). The inhibition of the MAOA isoform is measured by the method of Weyler et al. \((J. Biol Chem. 1985, 260, 13199-13207)\). The inhibition of the MAOB isoform is measured by the method of Uebelhack et al. \((Pharmacopsychiatry, 1998, 31, 187-192)\).

[0015] Examples of polymorphically-expressed cytochrome \( p_{450} \) isoforms in a mammalian subject include, but are not limited to, CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

[0016] The metabolic activities of liver microsomes, cytochrome \( p_{450} \) isoforms, and monoamine oxidase isoforms are measured by the methods described herein.

[0017] Examples of improved disorder-control and/or disorder-eradication endpoints, or improved clinical effects include, but are not limited to, blood pressure, systolic blood pressure, diastolic blood pressure, plasma aldosterone concentrations, urinary aldosterone concentrations, plasma 11-deoxycorticosterone concentrations, plasma Cortisol.

[00118] Examples of diagnostic hepatobiliary function endpoints include, but are not limited to, alanine aminotransferase ("ALT"), serum glutamic-pyruvic transaminase ("SGPT"), aspartate aminotransferase ("AST" or "SGOT"), ALT/AST ratios, serum aldolase, alkaline phosphatase ("ALP"), ammonia levels, bilirubin, gamma-glutamyl transpeptidase ("GGTP," "γ-GTP," or "GGT"), leucine aminopeptidase ("LAP"), liver biopsy, liver ultrasonography, liver nuclear scan, 5'-nucleotidase, and blood protein. Hepatobiliary endpoints are compared to the stated normal levels as given in "Diagnostic and Laboratory Test Reference", 4th edition, Mosby, 1999. These assays are run by accredited laboratories according to standard protocol.

[00119] Besides being useful for human treatment, certain compounds and formulations disclosed herein may also be useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

**Combination Therapy**

[00120] The compounds disclosed herein may also be combined or used in combination with other agents useful in the treatment of 11-β-hydroxylase-mediated disorders. Or, by way of example only, the therapeutic effectiveness of one of the compounds described herein may be enhanced by administration of an adjuvant (i.e., by itself the adjuvant may only have minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced).

[00121] Such other agents, adjuvants, or drugs, may be administered, by a route and in an amount commonly used therefor, simultaneously or sequentially with a compound as disclosed herein. When a compound as disclosed herein is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound disclosed herein may be utilized, but is not required.

[00122] In certain embodiments, the compounds disclosed herein can be combined with one or more adrenergic receptor antagonists, angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, anti-arrhythmics, anticoagulants, antiplatelet agents, beta-1
adrenergic receptor antagonists, calcium channel blockers, fibrates, platelet aggregation inhibitors, HMG-CoA reductase inhibitors, and diuretics.

[00123] In certain embodiments, the compounds disclosed herein can be combined with one or more adrenergic receptor antagonists, including, but not limited to, atenolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, timolol, doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, tolazoline, bucindolol, carvedilol, and labetalol.

[00124] In certain embodiments, the compounds disclosed herein can be combined with one or more angiotensin II receptor antagonists, including, but not limited to, candesartan, eprosartan, irbesartan, losartan, tasosartan, valsartan, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, molsidomin, and pentaerythritol tetranitrate.

[00125] In certain embodiments, the compounds disclosed herein can be combined with one or more angiotensin-converting enzyme inhibitors, including, but not limited to, captopril, enalapril, lisinopril, perindopril, ramipril, benazepril, cilazapril, fosinopril, trandolapril, spirapril, delapril, moexipril, temocapril, zofenopril, and imidapril.

[00126] In certain embodiments, the compounds disclosed herein can be combined with one or more anti-arrhythmics, including, but not limited to quinidine, procainamide, disopyramide, sparteine, ajmaline, prajmaline, lorajmine, lidocaine, mexiletine, tocainide, aprindine, propafenone, flecainide, lorcanide, encainide, amiodarone, bretylium tosilate, bunaftine, dofetilide, ibutilidem, moracizine, and cibenzoline.

[00127] In certain embodiments, the compounds provided herein can be combined with one or more anticoagulants, including, but not limited to, acenocoumarol, argatroban, bivalirudin, lepirudin, fondaparinux, heparin, phenindione, warfarin, and ximalagatran.

[00128] In certain embodiments, the compounds provided herein can be combined with one or more antiplatelet agents, including, but not limited to, abciximab, cilostazol, clopidogrel, dipyridamole, ticlopidine, and tirofibin.

[00129] In certain embodiments, the compounds disclosed herein can be combined with one or more beta-1 adrenergic receptor antagonists, including, but not limited to betaxolol, alprenolol, oxprenolol, pindolol, propranolol, timolol, sotalol, nadolol, mepindolol, carteolol, tertatolol, bopindolol, bupranolol, penbutolol, cloranolol, practolol, metoprolol, atenolol, acebutolol, bevantolol, bisoprolol, celiprolol, esmolol, epanolol, s-atenolol, nebivolol, talinolol, labetalol, and carvedilol.
In certain embodiments, the compounds disclosed herein can be combined with one or more calcium channel blockers, including, but not limited to amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, nilvadipine, manidipine, barnidipine, lercanidipine, cilnidipine, benidipine, mibefradil, verapamil, gallopamil, diltiazem, fendiline, bepridil, lidoflazine, and perhexiline.

In certain embodiments, the compounds provided herein can be combined with one or more fibrates, including, but not limited to, clofibrate, bezafibrate, aluminium clofibrate, gemfibrozil, fenofibrate, simfibrate, ronifibrate, ciprofibrate, etofibrate, and clofibrade.

In certain embodiments, the compounds disclosed herein can be combined with one or more platelet aggregation inhibitors, including, but not limited to acetylsalicylic acid/aspirin, aloxiprin, ditazole, carbasalate calcium, cloricromen, dipyridamol, indobufen, picotamide, triflusal, clopidogrel, ticlopidine, prasugrel, beraprost, prostacyclin, iloprost, and treprostinil.

In certain embodiments, the compounds disclosed herein can be combined with one or more HMG-CoA reductase inhibitors, including, but not limited to, atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

In certain embodiments, the compounds disclosed herein can be combined with one or more diuretics, including, but not limited to, bendroflumethiazide, hydroflumethiazide, hydrochlorothiazide, chlorothiazide, polythiazide, trichlormethiazide, cyclopentiazide, methyclothiazide, cyclothiazide, mebutizide, quinethazone, clopamide, chlortalidone, mefruside, clofenamide, metolazone, meticrane, xipamide, indapamide, clorexolone, fenquizone, mersalyl, theobromine, cicletanine, furosemide, bumetanide, piretanide, torasemide, etacrynic acid, tienilic acid, muzolimine, etozolin, spironolactone, potassium canrenoate, canrenone, and eplerenone.

The compounds disclosed herein can also be administered in combination with other classes of compounds, including, but not limited to, norepinephrine reuptake inhibitors (NRIs) such as atomoxetine; dopamine reuptake inhibitors (DARIs), such as methylphenidate; serotonin-norepinephrine reuptake inhibitors (SNRIs), such as milnacipran; sedatives, such as diazepam; norepinephrine-dopamine reuptake inhibitor (NDRIs), such as bupropion; serotonin-norepinephrine-dopamine-reuptake-inhibitors (SNDRIs), such as venlafaxine; monoamine oxidase inhibitors, such as selegiline; hypothalamic phospholipids; endothelin converting enzyme (ECE) inhibitors, such as phosphoramidon; opioids, such as
tramadol; thromboxane receptor antagonists, such as ifetroban; potassium channel openers; thrombin inhibitors, such as hirudin; hypothalamic phospholipids; growth factor inhibitors, such as modulators of PDGF activity; platelet activating factor (PAF) antagonists; anti-platelet agents, such as GPIIb/IIIa blockers (e.g., abdximab, eptifibatide, and tirofiban), P2Y(AC) antagonists (e.g., clopidogrel, ticlopidine and CS-747), and aspirin; anticoagulants, such as warfarin; low molecular weight heparins, such as enoxaparin; Factor Vila Inhibitors and Factor Xa Inhibitors; renin inhibitors; neutral endopeptidase (NEP) inhibitors; vasopepsidase inhibitors (dual NEP-ACE inhibitors), such as omapatrilat and gemopatrilat; HMG CoA reductase inhibitors, such as pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, nisvastatin, or nisbastatin), and ZD-4522 (also known as rosuvastatin, or atavastatin or visastatin); squalene synthetase inhibitors; fibrates; bile acid sequestrants, such as questran; niacin; anti-atherosclerotic agents, such as ACAT inhibitors; MTP Inhibitors; calcium channel blockers, such as amlodipine besylate; potassium channel activators; alpha-muscarinic agents; beta-muscarinic agents, such as carvedilol and metoprolol; antiarrhythmic agents; diuretics, such as chlorothiazide, hydrochlorothiazide, fiumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichioromethiazide, polythiazide, benzothiazide, ethacrylic acid, ticrynafen, chlorthalidone, furosenilde, musolimine, bumetanide, triamterene, amiloride, and spironolactone; thrombolytic agents, such as tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, and anisoylated plasminogen streptokinase activator complex (APSAC); anti-diabetic agents, such as biguanides (e.g. metformin), glucosidase inhibitors (e.g., acarbose), insulins, meglitinides (e.g., repaglinide), sulfonyleuases (e.g., glimepiride, glyburide, and glipizide), thiazolidinediones (e.g. troglitazone, rosiglitazone and pioglitazone), and PPAR-gamma agonists; mineralocorticoid receptor antagonists, such as spironolactone and eplerenone; growth hormone secretagogues; aP2 inhibitors; phosphodiesterase inhibitors, such as PDE III inhibitors (e.g., cilostazol) and PDE V inhibitors (e.g., sildenafil, tadalafil, vardenafil); protein tyrosine kinase inhibitors; antiinflammatories; antiproliferatives, such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil; chemotherapeutic agents; immunosuppressants; anticancer agents and cytotoxic agents (e.g., alkylating agents, such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes); antimetabolites, such as folate antagonists, purine analogues, and pyridine analogues; antibiotics, such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes, such as L-asparaginase; farnesyl-protein transferase inhibitors; hormonal agents, such as glucocorticoids (e.g., cortisone),

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estrogens/antiestrogens, androgens/antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, and octreotide acetate; microtubule-disruptor agents, such as eceinascidins; microtubule-stabilizing agents, such as pacitaxel, docetaxel, and epothilones A-F; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, and taxanes; and topoisomerase inhibitors; prenyl-protein transferase inhibitors; and cyclosporins; steroids, such as prednisone and dexamethasone; cytotoxic drugs, such as azathiprine and cyclophosphamide; TNF-alpha inhibitors, such as tenidap; anti-TNF antibodies or soluble TNF receptor, such as etanercept, rapamycin, and leflunimide; and cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib and rofecoxib; and miscellaneous agents such as, hydroxyurea, procarbazine, mitotane, hexamethylmelamine, gold compounds, platinum coordination complexes, such as cisplatin, satraplatin, and carboplatin.

[00136] Thus, in another aspect, certain embodiments provide methods for treating 11-β-hydroxylase-mediated disorders in a human or animal subject in need of such treatment comprising administering to the subject an amount of a compound disclosed herein effective to reduce or prevent the disorder in the subject, in combination with at least one additional agent for the treatment of the disorder that is known in the art. In a related aspect, certain embodiments provide therapeutic compositions comprising at least one compound disclosed herein in combination with one or more additional agents for the treatment of 11-β-hydroxylase-mediated disorders.

**General Synthetic Methods for Preparing Compounds**

[00137] Isotopic hydrogen can be introduced into a compound as disclosed herein by synthetic techniques that employ deuterated reagents, whereby incorporation rates are predetermined; and/or by exchange techniques, wherein incorporation rates are determined by equilibrium conditions, and may be highly variable depending on the reaction conditions. Synthetic techniques, where tritium or deuterium is directly and specifically inserted by tritiated or deuterated reagents of known isotopic content, may yield high tritium or deuterium abundance, but can be limited by the chemistry required. Exchange techniques, on the other hand, may yield lower tritium or deuterium incorporation, often with the isotope being distributed over many sites on the molecule.

[00138] The compounds as disclosed herein can be prepared by methods known to one of skill in the art and routine modifications thereof, and/or following procedures similar to those described in the Example section herein and routine modifications thereof, and/or procedures found in WO 2007024945, WO 201 1064376, and Merideth et al, ACS Med. Chem. Let.,
2013, 4(12), 1203-1207, which are hereby incorporated in their entirety, and references cited therein and routine modifications thereof. Compounds as disclosed herein can also be prepared as shown in any of the following schemes and routine modifications thereof.

[00139] The following schemes can be used to practice the present invention. Any position shown as hydrogen may optionally be replaced with deuterium.

**Scheme I**

![Diagram of Scheme I](image-url)
[00140] Compound 1 is treated with an appropriate protecting agent, such as triphenylmethane, in an appropriate solvent, such as pyridine, to give compound 2. Compound 2 is treated with an appropriate acid, such as anhydrous HCl, in an appropriate alcohol solvent, such as methanol, to give compound 3. Compound 4 is treated with an appropriate brominating agent, such as N-bromosuccinimide, in the presence of an appropriate radical initiator, such as benzoyl peroxide, in an appropriate solvent, such as carbon tetrachloride, at an elevated temperature, to give compound 5. Compound 3 is reacted with compound 5, in an appropriate solvent, such as acetonitrile, to give compound 6. Compound 6 is treated with an appropriate reducing agent, such as sodium borohydride, in an appropriate solvent, such as methanol, at a reduced temperature, to give compound 7. Compound 7 is treated with an appropriate chlorinating agent, such as thionyl chloride, in an appropriate solvent, such as dichloromethane, at a reduced temperature, to give compound 8. Compound 8 is treated with an appropriate base, such as potassium tert-butoxide, in an appropriate solvent, such as tetrahydrofuran, and then purified by chiral chromatography such as high performance liquid chromatography (HPLC), supercritical fluid chromatography (SFC), simulated moving bed chromatography (SMBC), or chiral resolution using an appropriate chiral acid, to give a compound of formula 1.

[00141] Deuterium can be incorporated to different positions synthetically, according to the synthetic procedures as shown in Scheme 1, by using appropriate deuterated intermediates. For example, to introduce deuterium at R1-R4, compound 1 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R7-R10, compound 4 with the corresponding deuterium substitutions can be used. To introduce deuterium at one or more positions of R5-R6, sodium borodeuteride can be used.

[00142] Deuterium can be incorporated to various positions having an exchangeable proton, via proton-deuterium equilibrium exchange. For example, such protons may be replaced with deuterium selectively or non-selectively through a proton-deuterium exchange method known in the art.

[00143] The invention is further illustrated by the following examples. All IUPAC names were generated using CambridgeSoft’s ChemDraw 10.0.
EXAMPLE 1

**(R)-4-(6,7-dihydro-5H-pyrrolo[1,2-b]imidazol-5-yl)-3-fluorobenzonitrile**

(osilodrostat)

Step 0

![Chemical structure](image)

[00144] 4-(bromomethyl)-3-fluorobenzonitrile: 3-Fluoro-4-methylbenzonitrile (40 g, 296 mmol), NBS (63.2 g, 356 mmol) and benzoyl peroxide (3.6 g, 14.8 mmol) were taken up in carbon tetrachloride (490 mL) and refluxed for 16 h. The mixture was allowed to cool to room temperature and filtered. The filtrate was concentrated and purified via flash column chromatography (0-5% EtOAc/hexanes) to give 4-(bromomethyl)-3-fluorobenzonitrile (35.4 g, 56%).

Step 1

![Chemical structure](image)

[00145] 2-(l-trityl-lH-imidazol-4-yl)acetic acid: Trityl chloride (40 g, 143.88 mmol, 1.2 equiv) was added to a suspension of (lH-imidazol-4-yl)acetic acid hydrochloride (20 g, 123.02 mmol, 1.0 equiv) in pyridine (200 mL). This was stirred at 50 °C for 16 h. Then the mixture was cooled and concentrated under vacuum and the crude product was purified by recrystallization from ethyl acetate (1000 ml) to afford 42 g (90%) of 2-[l-(triphenylmethyl)-lH-imidazol-4-yl] acetic acid as an off-white solid. LCMS (ESI): m/z = 369.2 [M+H]^+. 

LCMS (ESI): m/z = 369.2 [M+H]^+. 

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Step 2

[00146] 2-(1-trityl-lH-imidazol-4-yl)ethanol : 2-(l-Trityl-lH-imidazol-4-yl) acetic acid
(42 g, 114.00 mmol, 1.0 equiv) was suspended in THF (420 mL) and cooled to 0 °C. To this was added BH3 (1M in THF, 228.28 mL, 2.0 equiv). The clear solution obtained was stirred at 0 °C for 60 min, then warmed to room temperature until LCMS indicated completion of the reaction. The solution was cooled again to 0 °C and quenched carefully with water (300 mL). The resulting solution was extracted with ethyl acetate (3 x 100 mL) and the organic layers combined and dried over anhydrous Na2SO4 and evaporated to give a sticky residue which was taken up in ethanolamine (800 mL) and heated to 90 °C for 2 h. The reaction was transferred to a separatory funnel, diluted with EtOAc (1 L) and washed with water (3 x 600 mL). The organic phase was dried over anhydrous Na2SO4 and evaporated afford 35 g (87%) of 2-[l-(triphenylmethyl)-lH-imidazol-4-yl]ethanol as a white solid, which was used in the next step without further purification. LCMS (ESI) : m/z = 355.1 [M+H]+.

Step 3

[00147] 4-(2-(tert-butyldimethylsilyloxy)ethyl)-l-trityl-lH-imidazole : 2-(l-Trityl-lH-imidazol-4-yl) ethanol (35 g, 98.75 mmol, 1.00 equiv) was dissolved in DCM (210 mL). To this was added imidazole (19.95 g, 293.05 mmol, 3.00 equiv) and tert-butyldimethylsilylchloride (22.40 g, 149.27 mmol, 1.50 equiv). The mixture was stirred at room temperature until LCMS indicated completion of the reaction. Then the resulting solution was diluted with 500 mL of DCM. The resulting mixture was washed with water (3 x 300 mL). The residue was purified by a silica gel column, eluted with ethyl acetate/petroleum ether (1:4) to afford 40 g (77%) of 4-[2-[(tert-butyldimethylsilyl)oxy]ethyl]-l-(triphenylmethyl)-lH-imidazole as a white solid. LCMS (ESI) : m/z = 469.1 [M+H]+.
Step 4

[00148] 4-((5-(2-(tert-butyldimethylsilyloxy)ethyl)1H-imidazol-1-yl)methyl)-3-fluorobenzonitrile: 4-(2-((tert-Butyldimethylsilanyl)oxy)ethyl)-1H-imidazole (40 g, 85.34 mmol, 1.00 equiv) and 4-(Bromomethyl)-3-fluorobenzonitrile (27.38 g, 127.92 mmol, 1.50 equiv) obtained as a product of step 0, were dissolved in MeCN (480 mL) and DCM (80 mL), and stirred at room temperature for 48 h. Et$_2$NH (80 mL) and MeOH (480 mL) were then added and the solution was warmed 80 °C for 3 h. The solution was evaporated to dryness and the residue was purified via flash column chromatography (EtOAc/hexanes 1:5 to EtOAc) to afford 4-((5-(2-((tert-Butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)methyl)-3-fluorobenzonitrile (15 g, 50%). ¾ NMR (400 MHz, CDCl$_3$) δ: 7.67 (s, 1H), 7.43 (m, 2H), 6.98 (s, 1H), 6.88-6.79 (m, 1H), 5.34 (s, 2H), 3.79 (t, $J = 8.0$ Hz, 2H), 2.67 (t, $J = 8.0$ Hz, 2H), 0.88 (s, 9H), 0.02 (s, 6H). LCMS (ESI): m/z = 360.1 [M+H]$^+$. 

Step 5

Methyl 2-((5-(2-(tert-butyldimethylsilyloxy)ethyl)-1H-imidazol-1-yl)-2-(4-cyano-2-fluorophenyl)acetate: 4-((5-(2-((tert-Butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)methyl)-3-fluorobenzonitrile (15 g, 41.72 mmol, 1.00 equiv) was dissolved in anhydrous THF (150 mL) and stirred at -78 °C, then a THF solution of LiHMDS (75 mL, 1.80 equiv, 1.0 M) was added dropwise over 15 min. After 30 min, methyl cyanoformate (4.3 g, 45.50 mmol, 1.10 equiv) was added dropwise over 10 min and the solution was stirred at -78 °C for 2 h. The excess LiHMDS was quenched with aqueous saturated NH$_4$Cl and the mixture was allowed to warm to room temperature. The mixture was then diluted with EtOAc and washed...
with aqueous saturated NH₄Cl (200 mL). The organic layers was dried over anhydrous Na₂SO₄ and evaporated. The crude residue was purified via flash column chromatography (EtOAc/PE 3:10 to EtOAc) to give methyl 2-(5-(2-((tert-butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)-2-(4-cyano-2-fluorophenyl) acetate (15 g, 86%) as a light yellow solid.

\[ \text{NMR (400 MHz, CDCl}_3\text{)} \delta: 7.66 (s, 1H), 7.54-7.43 (m, 2H), 7.15 (t, J = 8.0 Hz 1H), 6.93 (s, 1H), 6.47 (s, 1H), 3.88-3.74 (m, 5H), 2.81-2.62 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H). \]

LCMS (ESI) : m/z = 418.2 [M+H]⁺.

Step 6

\[
\begin{array}{c}
\text{OTBS} \\
\text{NC} \\
\text{F} \\
\text{O} \\
\text{HCl (4M in dioxane)} \\
\text{6} \\
\text{step 6} \\
\text{NC} \\
\text{F} \\
\text{O} \\
\text{OH} \\
\text{7}
\end{array}
\]

Methyl 2-(4-cyano-2-fluorophenyl)-2-(5-(2-hydroxyethyl)-1H-imidazol-1-yl)acetate: Methyl 2-(5-(2-((tert-butyldimethylsilanyl)oxy)ethyl)-1H-imidazol-1-yl)-2-(4-cyano-2-fluorophenyl)acetate (15 g, 35.92 mmol, 1.00 equiv) was added to a solution of HCl in 1,4-dioxane (89 mL, 4.0 M, 359.2 mmol) at 0 °C and the mixture was allowed to warm to room temperature and stirred for 2 h. The solution was concentrated to dryness to give the crude alcohol, methyl 2-(4-cyano-2-fluorophenyl)-2-(5-(2-hydroxyethyl)-1H-imidazol-1-yl)acetate (10 g, 92%), which was used without further purification. LCMS: m/z = 304.0 [M+H]⁺.

Step 7

\[
\begin{array}{c}
\text{NC} \\
\text{F} \\
\text{O} \\
\text{H} \\
\text{7} \\
\text{step 7} \\
\text{NC} \\
\text{F} \\
\text{O} \\
\text{OMs} \\
\text{8}
\end{array}
\]

Methyl 2-(4-cyano-2-fluorophenyl)-2-(5-(2-(methylsulfonyloxy)ethyl)-1H-imidazol-1-yl)acetate: The crude methyl 2-(4-cyano-2-fluorophenyl)-2-(5-(2-hydroxyethyl)-1H-imidazol-1-yl)acetate (10 g, 32.97 mmol, 1.00 equiv) was dissolved in DCM (200 mL) and stirred at 0 °C, then Et₃N (20 g, 197.65 mmol, 6.00 equiv) and
methanesulfonyl chloride (4.52 g, 39.67 mmol, 1.20 equiv) were added. After completion of the reaction, the solution was diluted with DCM and washed with aqueous saturated NaHCO₃. The organic layer was dried over anhydrous Na₂SO₄, filtered and evaporated to give the crude methyl 2-(4-cyano-2-fluorophenyl)-2-(5-((methylsulfonyl)oxy)ethyl)-1H-imidazol-1-yl)acetate (11.43 g, 91%), which was used in the next step without further purification. LCMS (ESI) : m/z = 382.0 [M+H]⁺.

**Step 8**

[Methyl 5-(4-cyano-2-fluorophenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylate]: The crude methyl 2-(4-cyano-2-fluorophenyl)-2-(5-((methylsulfonyl)oxy)ethyl)-1H-imidazol-1-yl)acetate (11.43 g, 29.97 mmol, 1.00 equiv) was dissolved in MeCN (550 mL) and then K₂CO₃ (12.44 g, 90.01 mmol, 3.00 equiv), NaI (13.50 g, 90.00 mmol, 3.00 equiv) and Et₃N (9.09 g, 89.83 mmol, 3.00 equiv) were added. The reaction was stirred at 80 °C for 42 h. The mixture was filtered. The solids were washed with DCM. The filtrate was concentrated and purified by flash column chromatography (EtOAc) to give methyl 5-(4-cyano-2-fluorophenyl)-6,7-dihydro-5H-pyrrolo[1,2-c]imidazole-5-carboxylate (4.2 g, 49% in 3 steps).

[00153] 1H NMR (400 MHz, CDCB) δ: 7.61 (s, 1H), 7.47-7.47 (m, 2H), 6.88 (s, 1H), 6.79-6.75 (m, 1H), 4.17-4.12 (m, 1H), 3.87 (s, 3H), 3.78-3.70 (m, 1H), 3.08-3.02 (m, 1H), 2.84-2.71 (m, 2H). LCMS (ESI) : m/z = 286.0 [M+H]⁺.

**Step 9**

[10621]
4-(6,7-dihydro-5H-pyrrolo[1,2-elimidazol-5-yl)-3-fluorobenzonitrile: To a 40-mL sealed tube, was placed methyl 5-(4-cyano-2-fluorophenyl)-5H,6H-pyrrolo[1,2-c]imidazole-5-carboxylate (1 g, 3.51 mmol, 1.00 equiv), DMSO (10 mL), water (5 mL). The final reaction mixture was irradiated with microwave radiation for 40 min at 140 °C. The resulting solution was diluted with 100 mL of EtOAc. The resulting mixture was washed with (3 x 20 mL) brine, dried over anhydrous Na2SO4, filtered and concentrated. The residue was purified by a silica gel column, eluted with ethyl acetate/petroleum ether (4:1) to afford 420 mg (44%) of 5-(4-cyano-2-fluorophenyl)-5H,6H-pyrrolo[1,2-c]imidazole-5-carboxylic acid as a light yellow solid.

[00155] ¾ NMR (400 MHz, CDCl3) δ: 7.55-7.28 (m, 3H), 6.90-6.85 (m, 2H), 5.74-5.71 (m, 1H), 3.25-3.15 (m, 1H), 3.02-2.92 (m, 2H), 2.58-2.50 (m, 1H). LCMS (ESI) : m/z = 228.2 [M+H]+.

Resolution of the enantiomers of the title compound (300 mg) was performed by chiral HPLC: Column, Chiralpak IA2, 2*25cm, 20um; mobile phase, Phase A: Hex (50%, 0.1% DEA), Phase B: EtOH (50%) ; Detector, UV 254/220 nm to afford the (S)-enantiomer (RT = 17 min) and the (R)-enantiomer (97.6 mg, desired compound) (RT = 21 min).

[00157] ¾ NMR (400 MHz, DMSO-d6) δ: 7.98-7.95 (m, 1H), 7.70-7.69 (m, 1H), 7.50 (s, 1H), 6.87 (s, J = 8.0 Hz, 1H), 6.70 (s, 1H), 5.79-5.76 (m, 1H), 3.15-3.06 (m, 1H), 2.92-2.74 (m, 2H), 2.48-2.43 (m, 1H). LCMS (ESI) : m/z = 228.1 [M+H]+.
EXAMPLE 2

(R)-4-(6,7-dihydro-5H-pyrrolo[1,2-elimidazol-5-y1)-3-(\textsuperscript{2}H\textsubscript{2})fluorobenzonitrile

(osilodrostat-d\textsubscript{2})

As shown in the scheme, Example 2 was synthesized as follows:

Step 1

4-(6,7-dihydro-5H-pyrrolo[1,2-elimidazol-5-y1)-3-(\textsuperscript{2}H\textsubscript{2})fluorobenzonitrile: To a 40-mL sealed tube, was placed methyl 5-(4-cyano-2-fluorophenyl)-5H,6H,7H-pyrrolo[1,2-e]imidazole-5-carboxylate (1 g, 3.51 mmol, 1.00 equiv), DMSO (10 mL), D\textsubscript{2}O (5 mL). The final reaction mixture was irradiated with microwave radiation for 40 min at 140 °C. The resulting solution was diluted with 100 mL of EtOAc, washed with (3 x 20 mL) brine, dried over anhydrous Na2SO4, filtered and concentrated. The residue was purified by a silica gel column eluting with ethyl acetate/petroleum ether (4:1) to afford 420 mg (44%) of 4-(6,7-dihydro-5H-pyrrolo[1,2-e]imidazol-5-y1)-3-(\textsuperscript{2}H\textsubscript{2})fluorobenzonitrile as a light yellow solid.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 7.49-7.39 (m, 2H), 6.90-6.81 (m, 2H), 3.20-3.17 (m, 1H), 3.03-2.85 (m, 2H), 2.55-2.50 (m, 1H). LCMS (ESI) : m/z = 230.2 [M+H]\textsuperscript{+}. 
Step 2

\[ \text{2(R)-4-(6J-dihydro-5H-pyrrolori.2-elinTidazol-5-yl)-3-} (\text{H})\text{fluorobenzonitrile} : \]

Resolution of the racemate of the title compound (400 mg) was performed by chiral HPLC: Column, Chiralpak IA2, 2*25cm, 20um; mobile phase, Phase A: Hex (50%, 0.1% DEA), Phase B: EtOH (50%); Detector, UV 254/220 nm to afford the (S)-enantiomer (RT = 17 min) and the (R)-enantiomer (148.4 mg, desired compound) (RT = 21 min).

\[ \text{NMR} (400 \text{ MHz, DMSO-}d_6) \delta: 7.96-7.94 (d, J = 9.6 \text{ Hz, 1H}), 7.70-7.68 (d, J = 8.0 \text{ Hz, 1H}), 7.49 (s, 0.44H), 6.87 (t, J = 8.0 \text{ Hz, 1H}), 6.68 (s, 1H), 3.13-3.05 (m, 1H), 2.89-2.76 (m, 2H), 2.47-2.40 (m, 1H). \]

LCMS (ESI) : m/z = 230.1 [M+H]^+.

EXAMPLE 3

3-fluoro-4-[(5RV,6,7,7-\text{H},V5H,6H,7H-Derrlo}[1,2-climidazo]-5-ylbenzonitrile

\[ \text{(osilodrostat-d}^4) \]

Step 1

\[ \text{2-}[1-(triphenylmethyl)(2-} (\text{H})\text{-imidazol-4-yl})\text{-acetic acid: To a suspension of 2-}[1-(triphenylmethyl)-\text{H-imidazol-4-yl}]\text{acetic acid (31 g, 84.14 mmol, 1.00 equiv) in D}_2\text{O (250 mL) were added NaOD (3M in D2O) (33.7 mL, 1.20 equiv) and TBAB (541 mg, 1.68 mmol, 0.02 equiv). The resulting solution was stirred for 18 h at 100 \text{ °C. The reaction} } \]
progress was monitored by H-NMR. The pH value of the solution was adjusted to 5 with HCl (0.5 mol/L). The solids were collected by filtration, dried in an oven under reduced pressure to afford 29 g (93%) of 2-[l-(triphenylmethyl)(2-^3^H)-lH-imidazol-4-yl](^3^H)acetic acid as a white solid. 

\[ \text{NMR (400 MHz, CDCl)}^* \]

1.11 (brs, 1H), 7.38-7.36 (m, 9H), 7.17-7.10 (m, 6H), 6.75 (s, 1H).

**Step 2**

\[
\begin{array}{c}
\text{Trt} \\
\text{D} \\
\text{D} \\
\text{OH} \\
\end{array}
\xrightarrow{\text{BD3/THF}}
\begin{array}{c}
\text{Trt} \\
\text{D} \\
\text{D} \\
\text{OH} \\
\end{array}
\]

[001 64] 2-l1-(triphenylmethyl)(2-^3^H)-1H-imidazol-4-yl (^3^H)ethan-1-ol: To a solution of 2-[l-(triphenylmethyl)(2-^3^H)-lH-imidazol-4-yl](^3^H)acetic acid (28 g, 75.38 mmol, 1.00 equiv) in tetrahydrofuran (200 mL) was added a solution of BD3 (1M in tetrahydrofuran) (94 mL, 1.20 equiv) at 0 °C in 20 min. The resulting solution was stirred for 2 h at 25 °C. The reaction was then quenched by the addition of 10 mL of D2O. The resulting solution was diluted with 100 mL of water. The resulting solution was extracted with 3 x 100 mL of ethyl acetate and the organic layers combined, washed with 2 x 100 mL of brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was dissolved in ethanalamine (100 mL). The resulting solution was allowed to react, with stirring, for an additional 2 h while the temperature was maintained at 90 °C. The resulting solution was diluted with EtOAc (1 L) and washed with water (3 x 200 mL), brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford 24 g (89%) of 2-[l-(triphenylmethyl)(2-^3^H)-lH-imidazol-4-yl](^3^H)ethan-1 -ol as a white solid. LC-MS: m/z = 360 [M+H]^+.

**Step 3**

\[
\begin{array}{c}
\text{Trt} \\
\text{D} \\
\text{D} \\
\text{OH} \\
\end{array}
\xrightarrow{\text{TBSC/Imidazole}}
\begin{array}{c}
\text{Trt} \\
\text{D} \\
\text{D} \\
\text{OTBS} \\
\end{array}
\]

[001 65] 4-r2-r(tert-butyldimethylsilyl)oxy1 (^3^H)ethyll-l-(triphenylmethyl)(2-^3^H)-IH-imidazole: To a solution of 2-[l-(triphenylmethyl)(2-^3^H)-lH-imidazol-4-yl](^3^H)ethan-1 -ol
(24 g, 66.76 mmol, 1.00 equiv) in N,N-dimethylformamide (200 mL) were added imidazole (13.7 g, 201.47 mmol, 3.00 equiv) and TBSCl (11.4 g, 76.00 mmol, 1.20 equiv). The resulting solution was stirred for 12 h at 25 °C. The reaction progress was monitored by LCMS. The reaction was then quenched by the addition of 400 mL of water/ice. The resulting solution was extracted with ethyl acetate (3 x 200 mL) and the organic layers were combined, washed with sat. NaHCO₃ (2 x 100 mL), brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by a silica gel column eluting with ethyl acetate/petroleum ether (1:2) to afford 18.3 g (58%) of 4-[2-[(tert-butyldimethylsilyl)oxy](H₄)ethyl]-1-(triphenylmethyl)(2-²H)-IH-imidazole as a light yellow solid. LC-MS: m/z = 474 [M+H]⁺.

Step 4

[00166] 4-[5-12-[(tert-butyldimethylsilyl)oxy](H₄)ethyl]-1H-imidazol-1-vDMethyl-3-fluorobenzonitrile: To a solution of 4-[2-[(tert-butyldimethylsilyl)oxy](H₄)ethyl]-1-(triphenylmethyl)(2-²H)-IH-imidazole (18.3 g, 38.63 mmol, 1.00 equiv) in CIL CN (300 mL), dichloromethane (50 mL) was added 4-(bromomethyl)-3-fluorobenzonitrile (10.7 g, 49.99 mmol, 1.30 equiv). The resulting solution was stirred for 40 h at 25 °C and then concentrated under vacuum. The residue was dissolved in 180 mL of methanol, TEA (38.6 mL, 10.00 equiv) was added. The resulting solution was allowed to react, with stirring, for an additional 3 h while the temperature was maintained at 80 °C. The reaction progress was monitored by LCMS. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 400 mL of ethyl acetate, washed with 2 x 200 mL of brine, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by a silica gel column, eluted with ethyl acetate/petroleum ether (1:1) to afford 9 g (64%) of 4-[5-12-[(tert-butyldimethylsilyl)oxy](H₄)ethyl]-1H-imidazol-1-yl)methyl]-3-fluorobenzonitrile as a light yellow solid. ¾ NMR (400 MHz, CDCl₃) δ: 7.59 (s, 1H), 7.44-7.41 (m, 2H), 6.97 (s,
1H), 6.82-6.28 (m, 1H), 5.33 (s, 2H), 0.88 (s, 9H), 0.02 (s, 6H). LC-MS: m/z = 364 [M+H]⁺.

Step 5

Methyl2-(5-[2-(tert-butyldimethylsilyloxyl(\(^{1}H\))ethyl]-lH-imidazol-1-yl)-2-(4-cyano-2-fluorophenyl)acetate: To a solution of 4-[[5-[2-[(tert-butyldimethylsilyl)oxy] (\(^{3}H\))ethyl]-lH-imidazol-1-yl]methyl]-3-fluorobenzonitrile (4.6 g, 12.65 mmol, 1.00 equiv) in tetrahydrofuran (120 mL) was added a solution of LiHMDS (1 M in tetrahydrofuran) (23 mL, 1.80 equiv) dropwise with stirring at -78 °C in 20 min. The resulting solution was stirred for 30 min at -78 °C. Then a solution of chloro(methoxy)methanone (1.4 g, 14.82 mmol, 1.10 equiv) in tetrahydrofuran (30 mL) was added dropwise with stirring at -78 °C in 10 min. The resulting solution was allowed to react, with stirring, for an additional 2 h while the temperature was maintained at 0-10 °C. The reaction progress was monitored by LCMS. The reaction was then quenched by the addition of 50 mL of sat. NH₄Cl. The resulting solution was extracted with ethyl acetate (3 x 50 mL) and the organic layers were combined, washed with sat. NH₄Cl (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by a silica gel column eluting with ethyl acetate/petroleum ether (1:3) to afford 4.6 g (86%) of methyl 2-(5-[2-[(tert-butyldimethylsilyl)oxy](\(^{3}H\))ethyl]-lH-imidazol-1-yl)-2-(4-cyano-2-fatty oils, liquid paraffin, or liquid polyethLC-MS: m/z = 422 [M+H]⁺.

Step 6
Methyl 2-(4-cyano-2-fluorophenyl)-2-(4-((tert-butyldimethylsilyl)oxy)(4H)ethyl)-1H-imidazol-1-yl acetate: Methyl 2-(5-[2-[(tert-butyldimethylsilyl)oxy](4H)ethyl]-1H-imidazol-1-yl)-2-(4-cyano-2-fluorophenyl)acetate (4.6 g, 10.91 mmol, 1.00 equiv) was dissolved in HCl (4M in dioxane) (50 mL). The resulting solution was stirred for 2 h at 25 °C. The reaction progress was monitored by LCMS. The resulting mixture was concentrated under vacuum to afford 4.3 g (crude) of methyl 2-(4-cyano-2-fluorophenyl)-2-[5-[2-hydroxy(4H)ethyl]-1H-imidazol-1-yl]acetate as a light yellow solid, which was used directly to the next step. LC-MS: m/z = 308 [M+H]+.

Step 7

Methyl 2-(4-cyano-2-fluorophenyl)-2-(4-((tert-butyldimethylsilyl)oxy)(4H)ethyl)-1H-imidazol-1-yl acetate: To a solution of methyl 2-(4-cyano-2-fluorophenyl)-2-[5-[2-hydroxy(4H)ethyl]-1H-imidazol-1-yl]acetate (4.3 g, 13.99 mmol, 1.00 equiv) in dichloromethane (30 mL) was added TEA (7.1 g, 70.17 mmol, 5.00 equiv). Then a solution of MsCl (1.76 g, 15.44 mmol, 1.10 equiv) in dichloromethane (5 mL) was added dropwise with stirring at 0 °C in 10 min. The resulting solution was stirred for 2 h at 25 °C. The resulting solution was diluted with 100 mL of DCM, washed with sat. NaHCO3 (2 x 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford 3.6 g (67%) of methyl 2-(4-cyano-2-fluorophenyl)-2-[5-[2-(methanesulfonyloxy)(4H)ethyl]-1H-imidazol-1-yl] acetate as a yellow solid, which was used directly in the next step.

Step 8
Methyl 5-(4-cyano-2-fluorophenyl)-6,6,7,7-^4^H^4^,6,7H-pyrrolo[1,2-c]imidazole-5-carboxylate: To a solution of methyl 2-(4-cyano-2-fluorophenyl)-2-[5-[2-(methanesulfonyloxy)(^4^H_2)ethyl]-1H-imidazol-1-yl]acetate (3.5 g, 9.08 mmol, 1.00 equiv) in CH3CN (100 mL) were added potassium carbonate (3.76 g, 27.20 mmol, 3.00 equiv), TEA (2.75 g, 27.18 mmol, 3.00 equiv) and NaI (4.1 g, 27.33 mmol, 3.00 equiv). The resulting solution was stirred for 12 h at 80 °C. The reaction progress was monitored by LCMS. The solids were filtered out. The resulting mixture was concentrated under vacuum. The residue was purified by a silica gel column eluting with ethyl acetate to afford 1 g (38%) of methyl 5-(4-cyano-2-fluorophenyl)(6,6,7,7-^4^H^4^)-5H,6H,7H-pyrrolo[1,2-c]imidazole-5-carboxylate as a yellow solid. ^1^H NMR (400 MHz, CDCl_3) δ: 7.61 (s, 1H), 7.49-7.41 (m, 2H), 6.87 (s, 1H), 6.82-6.72 (m, 1H), 3.86 (s, 3H). LC-MS: m/z = 290 [M+H]^+.

Step 9

3-fluoro-4-(6,6,7,7-^4^H^4^)-5H,6H,7H-pyrrolo[1,2-c]imidazole-5-yl]benzonitrile: To a 40-mL sealed tube, was placed methyl 5-(4-cyano-2-fluorophenyl)(6,6,7,7-^4^H^4^)-5H,6H,7H-pyrrolo[1,2-c]imidazole-5-carboxylate (1 g, 3.46 mmol, 1.00 equiv), DMSO (15 mL), D_2^O (5 mL). The final reaction mixture was irradiated with microwave radiation for 2 h at 160 °C. The reaction progress was monitored by LCMS. The reaction was then quenched by the addition of 60 mL of water/ice. The resulting solution was extracted with ethyl acetate (3 x 50 mL) and the organic layers were combined, washed with brine (2 x 50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by a silica gel column eluting with ethyl acetate to afford 700 mg (88%) of 3-fluoro-4-[(6,6,7,7-^4^H^4^)-5H,6H,7H-pyrrolo[1,2-c]imidazole-5-yl]benzonitrile as a yellow solid. LC-MS: m/z= 232 [M+H]^+.
Step 10

3-fluoro-4-\((5R)-(6,6,7,7-^4\text{H}_4)-5H.6H.7H-pyrrolo[1,2-c]imidazol-5-\)ylnitrobenzonitrile: 700 mg of racemic product was dissolved in methanol (2 mL) and purified by chiral HPLC: Column, Chiralpak IA2, 2*25 cm, 20um; mobile phase, Phase A: Hex (50%, 0.1% DEA), Phase B: EtOH (50%); Detector, UV 254/220 nm, afford 210 mg (30%) of 3-fluoro-4-\((5R)-(6,6,7,7-^4\text{H}_4)-5H.6H.7H-pyrrolo[1,2-c]imidazol-5-\)ylnitrobenzonitrile (RT = 21 min, desired product) as a white solid and 200 mg (29%) of 3-fluoro-4-\((5S)-(6,6,7,7-^4\text{H}_4)-5H.6H.7H-pyrrolo[1,2-c]imidazol-5-\)ylnitrobenzonitrile (RT = 17 min) as a white solid. ¾NMR (400 MHz, CDCl₃) δ: 7.47-7.41 (m, 3H), 6.87-6.82 (m, 2H), 5.69 (s, 1H). LC-MS: m/z = 232 [M+H]⁺.

The following compounds can generally be made using the methods described above. It is expected that these compounds when made will have activity similar to those described in the examples above.
In certain embodiments, the compound is an isolated enantiomer of a compound disclosed herein. In further embodiments, the enantiomer is the (R) enantiomer. For example, the compound may be chosen from:
Changes in the metabolic properties of the compounds disclosed herein as compared to their non-isotopically enriched analogs can be shown using the following assays. Compounds listed above which have not yet been made and/or tested are predicted to have changed metabolic properties as shown by one or more of these assays as well.

**Biological Activity Assays**

*In vitro* Liver Microsomal Stability Assay

Liver microsomal stability assays are conducted at 1 mg per mL liver microsome protein with an NADPH-generating system in 2% NaHCO₃ (2.2 mM NADPH, 25.6 mM glucose 6-phosphate, 6 units per mL glucose 6-phosphate dehydrogenase and 3.3 mM MgCh). Test compounds are prepared as solutions in 20% acetonitrile-water and added to the assay mixture (final assay concentration 5 microgram per mL) and incubated at 37 °C. Final concentration of acetonitrile in the assay should be ≤8%. Aliquots (50 µL) are taken out at times 0, 15, 30, 45, and 60 min, and diluted with ice cold acetonitrile (200 µL) to stop the reactions. Samples are centrifuged at 12,000 RPM for 10 min to precipitate proteins. Supematants are transferred to microcentrifuge tubes and stored for LC/MS/MS analysis of the degradation half-life of the test compounds.
In vitro metabolism using human cytochrome P450 enzymes

[00177] The cytochrome P450 enzymes are expressed from the corresponding human cDNA using a baculovirus expression system (BD Biosciences, San Jose, CA). A 0.25 milliliter reaction mixture containing 0.8 milligrams per milliliter protein, 1.3 millimolar NADP⁺, 3.3 millimolar glucose-6-phosphate, 0.4 U/mL glucose-6-phosphate dehydrogenase, 3.3 millimolar magnesium chloride and 0.2 millimolar of a compound of Formula I, the corresponding non-isotopically enriched compound or standard or control in 100 millimolar potassium phosphate (pH 7.4) is incubated at 37 °C for 20 min. After incubation, the reaction is stopped by the addition of an appropriate solvent (e.g., acetonitrile, 20% trichloroacetic acid, 94% acetonitrile/6% glacial acetic acid, 70% perchloric acid, 94% acetonitrile/6% glacial acetic acid) and centrifuged (10,000 g) for 3 min. The supernatant is analyzed by HPLC/MS/MS. Compounds disclosed herein are expected to have activity in this assay as demonstrated by reduced metabolism by one or more cytochrome P450 enzymes of deuterated compound as compared to the non-isotopically enriched compound.

<table>
<thead>
<tr>
<th>Cytochrome P450</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Phenacetin</td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Coumarin</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>[13C]-(S)-mephenytoin</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Dielofenac</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>[13C]-(S)-mephenytoin</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>(+/-)-Bufuralol</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>Chlorzoxazone</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Testosterone</td>
</tr>
<tr>
<td>CYP4A</td>
<td>[13C]-Lauric acid</td>
</tr>
</tbody>
</table>

In vitro CYP2C19 Stability Assay

[00178] Recombinant CYP2C19 stability assays are conducted at an enzyme concentration of 70 pmol per mL with NADPH (2mM, pH 7.4). Test compounds are typically prepared as acetonitrile with 5% DMSO and added to the assay mixture (luM, final concentration in incubation) to be incubated at 37 °C. Reactions are initiated with the addition of NADPH cofactor and are stopped at 0, 30, 60, 90 or 120 min after cofactor addition with stop reagent, acetonitrile. After quenching, plates containing samples are vibrated for 10 min (600
η/min) and then centrifuged at 5594 g for 15 min. Supernatant fractions are analyzed by LC-MS/MS to determine the percent remaining and estimate the degradation half-life of the test compounds. Results are given below.

<table>
<thead>
<tr>
<th>Example</th>
<th>half-life % change over d0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>-69.0</td>
</tr>
<tr>
<td>3</td>
<td>44.8</td>
</tr>
</tbody>
</table>

Other compounds disclosed herein are expected to have activity similar to or greater than the compounds disclosed above.

**Monoamine Oxidase A Inhibition and Oxidative Turnover**

The procedure is carried out using the methods described by Weyler, *Journal of Biological Chemistry* 1985, 260, 13199-13207, which is hereby incorporated by reference in its entirety. Monoamine oxidase A activity is measured spectrophotometrically by monitoring the increase in absorbance at 314 nm on oxidation of kynuramine with formation of 4-hydroxyquinoline. The measurements are carried out, at 30 °C, in 50mM NaPi buffer, pH 7.2, containing 0.2% Triton X-100 (monoamine oxidase assay buffer), plus 1 mM kynuramine, and the desired amount of enzyme in 1 mL total volume.

**Monoamine Oxidase B Inhibition and Oxidative Turnover**

The procedure is carried out as described in Uebelhack, *Pharmacopsychiatry* 1998, 37(5), 187-192, which is hereby incorporated by reference in its entirety.

**In Vitro Human and Rat CYP1B2 and CYP1B1 Inhibition Assays**

The procedure may be carried out as described in Merideth et al, ACS Med. Chem. Let, 2013, 4(12), 1203-1207, or as described in WO 201301064376, both of which are hereby incorporated by reference in their entireties.

The cell line NCI-H295R was originally isolated from an adrenocortical carcinoma and has been characterized in the literature through the stimulable secretion of steroid hormones and the presence of the enzymes essential for steroidogenesis. Thus, the NCI-H295R cells have CYP1B1 (steroid 11β-hydroxylase). The cells show the physiological property of zonally undifferentiated human fetal adrenocortical cells which,
however, have the capacity to produce the steroid hormones which are formed in the three, phenotypically distinguishable zones in the adult adrenal cortex.

[00184] The NCI-H295R cells (e.g., from American Type Culture Collection, ATCC, Rockville, MD, USA) are grown in Dulbecco's Modified Eagle/Ham's F-12 Medium (DME/F12), which has been supplemented with Ulroser SF Serum (e.g., from Soprachem, Cergy-Saint-Christophe, France), insulin, transferrin, selenite (e.g., from 1-T-S, Becton Dickinson Biosciences, Franklin lakes, NJ, USA) and antibiotics in 75 cm² cell culture vessels at 37°C and in a 95% air-5% carbon dioxide atmosphere. The cells are subsequently transferred for colony formation into a 24-well incubation vessel. They are cultivated there in DME/F12 medium, which is then supplemented with 0.1% bovine serum instead of Ultroser SF for 24 hours. The experiment is initiated by cultivating the cells in DME/F12 medium which is supplemented with 0.1% bovine serum albumin and test compound, in the presence or absence of cell stimulants, for 72 hours. The test substance is added in a concentration range from 0.2 nanomolar to 20 millimolar. Cell stimulants which can be used are angiotensin 11 (1 D or 100 nanomolar), potassium ions (16 millimolar), forskolin (10 micromolar) or a combination of two stimulants.

[00185] The excretion of aldosterone, Cortisol, corticosterone and estradiol/estrone into the culture medium can be detected and quantified by commercially available, specific monoclonal antibodies in radioimmunoassays in accordance with the manufacturer's instructions.

[00186] Inhibition of the release of certain steroids can be used as a measure of the respective enzyme inhibition by the added test compounds. The dose-dependent inhibition of enzymatic activity by a compound is calculated by means of an inhibition plot which is characterized by an IC50.

[00187] The IC50 values for active test compounds may be ascertained by a simple linear regression analysis in order to construct inhibition plots without data weighting. The inhibition plot is calculated by fitting a 4-parameter logistic function to the raw data points using the least squares method. The equation of the 4-parameter logistic function is calculated as follows: \( Y = \frac{(d-a)}{(1 + (x/c)b)} + a \), where: a - minimum data level, b = gradient, I c = ICED, d = maximum data level, x = inhibitor concentration.

[00188] The inhibition activity of aldosterone production can also be expressed in percentage inhibition (% inhibition) at a given concentration (e.g. % inhibition at 1 µM), which is the aldosterone level when the cell is treated with the given concentration of test compound (e.g. concentration of 1µM) versus the aldosterone excretion when cell is free of
test compound. Percent (%) inhibition aldosterone production = \([(Y-X)/Y]\) x 100 wherein X is the level of aldosterone when the cell is treated with test compound, and Y is the level of aldosterone when the cell is free of test compound.

The inhibition activity of CYP1B1 production can also be expressed in percentage inhibition (% inhibition) at a given concentration (e.g. % inhibition at 1 µM), which is the Cortisol level when cell is treated with the given concentration of test compound (e.g. concentration of 1µM) versus the Cortisol excretion when cell is free of test compound. Percent (%) inhibition Cortisol production = \([(Y'-X')/Y']\) x 100 wherein X’ is the level of Cortisol when the cell is treated with test compound; and Y is the level of Cortisol when the cell is free of test compound.

Compounds disclosed herein are expected to exhibit inhibitory efficacy in this assay.

In Vitro Aldosterone Synthase Assay

The procedure is carried out as described in WO 201 1064376, which is hereby incorporated by reference in its entirety. Aldosterone synthase inhibitory activities in vitro can be determined by the following assay. Human adrenocortical carcinoma NCI-H295R cell line may be obtained from American Type Culture Collection (Manassas, VA). Insulin/transferrin/selenium (ITS)-A supplement (100x), DMEM/F-12, antibiotic/antimycotic (100x), and fetal bovine serum (FBS) may be purchased from Invitrogen (Carlsbad, CA). Anti-mouse PVT scintillation proximity assay (SPA) beads and NBS 96-well plates may be obtained from GE Health Sciences (Piscataway, NJ) and Corning (Acton, MA), respectively. Solid black 96-well flat bottom plates were purchased from Costar (Coming, NY).

Aldosterone and angiotensin (Ang II) may be purchased from Sigma (St. Louis, MO). D-[l,2,6,7-3H(N)]aldosterone may be acquired from PerkinElmer (Boston, MA). Nu-serum was a product of BD Biosciences (Franklin Lakes, NJ).

For in vitro measurement of aldosterone activity, human adrenocortical carcinoma NCI-H295R cells are seeded in NBS 96-well plates at a density of 25,000 cells/well in 100 µl of a growth medium containing DMEM/F12 supplemented with 10% FCS, 2,5% Nu-serum, 1 pg ITS/ml, and 1x antibiotic/antimycotic. The medium is changed after culturing for 3 days at 37 °C under an atmosphere of 5% C02/95% air. On the following day, cells are rinsed with 100 µl of phosphate-buffered saline (PBS) and incubated with 100 µl of treatment medium containing 1 µM Ang II and a compound at different concentrations in quadruplicate wells at 37 °C for 24 hr. At the end of incubation, 50 µl of medium is withdrawn from each well for
measurement of aldosterone production by an SPA using mouse anti-aldosterone monoclonal antibodies.

[00193] Measurement of aldosterone activity can also be performed using a 96-well plate format. Each test sample is incubated with 0.02 pCi of D-[1,2,6,7-3H(N)]aldosterone and 0.3 pg of anti-aldosterone antibody in PBS containing 0.1% Triton X-00, 0.1% bovine serum albumin, and 12% glycerol in a total volume of 200 µl at room temperature for 1 hr. Anti-mouse PVT SPA beads (50 µl) are then added to each well and incubated overnight at room temperature prior to counting in a Microbeta plate counter. The amount of aldosterone in each sample is calculated by comparing with a standard curve generated using known quantities of the hormone. Compounds disclosed herein are predicted to have activity in this assay.

Clinical Study in Patients with Primary Hypertension
[00194] The procedure is carried out as described in Calhoun et al, Circulation, 2011, 124(18), 1945-1955, which is hereby incorporated by reference in its entirety. Compounds disclosed herein are expected to be effective in reducing primary hypertension.

Clinical Study in Patients With Cushing's Disease
[00195] The procedure is carried out as described in Bertagna et al, J. Clin. Endocrinol. Metab., 2014, 99(4), 1375-1383, which is hereby incorporated by reference in its entirety. Compounds disclosed herein are expected to be effective in treating Cushing’s disease.

Clinical Study in Patients With Hypertension
[00196] The procedure is carried out as described in Andersen et al, J. Clin. Hypertension, 2012, 14(9), 580-587, which is hereby incorporated by reference in its entirety. Compounds disclosed herein are expected to be effective in reducing hypertension.

Rat Model of Acute Secondary Hyperaldosteronism
[00197] The procedure is carried out as described in WO 2007024945, which is hereby incorporated by reference in its entirety.

[00198] Test compounds (i.e., potential aldosterone synthase inhibitors) are profiled in vivo in a conscious rat model of acute secondary hyperaldosteronism. Wild-type rats are instrumented with chronically indwelling arterial and venous cannulas, which are exteriorized through atether/swivel system. The ambulatory rats are housed in specialized cages to allow
blood sampling and parenteral drug administration without disturbing the animals.

Angiotensin II is continuously infused intravenously at a level sufficient to elevate plasma aldosterone concentration (PAC) by ~200-fold to 1-5 nM. This PAC increase is sustained at stable level for at least 8-9 hours. Test compounds are administered p.o. (via oral gavage) or parenterally (via the arterial catheter) after one hour of angiotensin II infusion at a time when PAC has increased to a steady-state level. Arterial blood samples are collected before and at various times (up to 24 hours) after test agent administration for later determination of PAC and concentration of test agent. From these measurements, various parameters can be derived, e.g., 1) onset and duration of PAC reduction by the test agent, 2) pharmacokinetic parameters of the test agent such as half-life, clearance, volume of distribution, and oral bioavailability, 3) dose/PAC response, dose/test-agent concentration, and test-agent concentration/PAC response relationships, and 4) dose- and concentrationpotencies and efficacy of the test agent. A successful test compound decreases PAC in a dose- and time-dependent fashion, e.g. in the dose range of about 0.01 to about 10 mg/kg.

**In Vitro Aromatase Inhibition Activity**

[00199] The procedure is carried out as described in WO 2007024945, which is hereby incorporated by reference in its entirety. Compounds disclosed herein are predicted to have activity in this assay.

[00200] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.
CLAIMS

What is claimed is:

1. A compound of structural Formula I

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 (I)
```

or a salt thereof, wherein:

Ri-Rio are independently chosen from hydrogen and deuterium; and

at least one of Ri-Rio is deuterium or contains deuterium.

2. The compound, or a salt thereof, as recited in claim 1, wherein Ri is deuterium.
3. The compound, or a salt thereof, as recited in claim 1, wherein R7 is deuterium.
4. The compound, or a salt thereof, as recited in claim 1, wherein Ri and R7 are deuterium.
5. The compound, or a salt thereof, as recited in claim 1, wherein R3 and R4 are deuterium.
6. The compound, or a salt thereof, as recited in claim 1, wherein R5 and R6 are deuterium.
7. The compound, or a salt thereof, as recited in claim 1, wherein R3-R6 are deuterium.
8. The compound, or a salt thereof, as recited in claim 1, wherein Ri and R3-R6 are deuterium.
9. The compound, or a salt thereof, as recited in claim 1, wherein R7 and R3-R6 are deuterium.
10. The compound, or a salt thereof, as recited in claim 1, wherein Ri, R7, and R3-R6 are deuterium.
11. The compound, or a salt thereof, as recited in any one of claims 1-9, wherein at least one of R1-R10 independently has deuterium enrichment of no less than about 1%.
12. The compound, or a salt thereof, as recited in any one of claims 1-9, wherein at least one of R1-R10 independently has deuterium enrichment of no less than about 10%.
13. The compound, or a salt thereof, as recited in any one of claims 1-9, wherein at least one of R1-R10 independently has deuterium enrichment of no less than about 50%.
14. The compound, or a salt thereof, as recited in any one of claims 1-9, wherein at least one of Ri-Rio independently has deuterium enrichment of no less than about 90%.

15. The compound, or a salt thereof, as recited in any one of claims 1-9, wherein at least one of Ri-Rio independently has deuterium enrichment of no less than about 98%.

16. The compound as recited in Claim 1 wherein the compound has a structural formula chosen from

![Chemical Structures](image-url)
17. The compound as recited in Claim 1 wherein the compound has a structural formula chosen from thereof.

, and , or a salt
18. The compound as recited in Claim 1 wherein the compound has a structural formula that is

19. The compound as recited in claim 16, 17, or 18, wherein each position represented as D has deuterium enrichment of no less than about 1%.

20. The compound as recited in claim 16, 17, or 18, wherein each position represented as D has deuterium enrichment of no less than about 10%.

21. The compound as recited in claim 16, 17, or 18, wherein each position represented as D has deuterium enrichment of no less than about 50%.

22. The compound as recited in claim 16, 17, or 18, wherein each position represented as D has deuterium enrichment of no less than about 90%.

23. The compound as recited in claim 16, 17, or 18, wherein each position represented as D has deuterium enrichment of no less than about 98%.

24. A pharmaceutical composition comprising a compound, or a salt thereof, as recited in any of Claims 1-23 together with a pharmaceutically acceptable carrier.

25. A method of treatment of an 11-β-hydroxylase-mediated disorder comprising the administration of a therapeutically effective amount of a compound, or a salt thereof, as recited in any of Claims 1-23 to a patient in need thereof.

26. The method as recited in Claim 25 wherein the disorder is chosen from Cushing’s disease, primary aldosteronism, hypertension, drug-resistant hypertension, essential hypertension,
hypokalemia, hypertension, congestive heart failure, acute heart failure, heart failure, cachexia, acute coronary syndrome, chronic stress syndrome, Cushing's syndrome, metabolic syndrome, hypercortisolemia, atrial fibrillation, renal failure, chronic renal failure, restenosis, sleep apnea, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart disease, increased formation of collagen, cardiac or myocardial fibrosis and/or remodeling following hypertension and endothelial dysfunction, Conn's disease, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, arrhythmia, diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertrophic cardiomyopathy, sudden cardia death, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, fibrinoid, necrosis of coronary arteries, ectopic ACTH syndrome, change in adrenocortical mass, primary pigmented nodular adrenocortical disease (PPNAD), Carney complex (CNC), anorexia nervosa, chronic alcoholic poisoning, nicotine withdrawal syndrome, cocaine withdrawal syndrome, post-traumatic stress syndrome, cognitive impairment after a stroke or cortisol-induced mineral corticoid excess, ventricular arrythmia, estrogen-dependent disorders, gynecomastia, osteoporosis, prostate cancer, endometriosis, uterine fibroids, dysfunctional uterine bleeding, endometrial hyperplasia, polycystic ovarian disease, infertility, fibrocystic breast disease, breast cancer, and fibrocystic mastopathy.

27. The method as recited in Claim 22 further comprising the administration of an additional therapeutic agent.

28. The method as recited in Claim 27 wherein the additional therapeutic agent is chosen from adrenergic receptor antagonists, angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, anti-arrhythmics, anticoagulants, antiplatelet agents, beta-1 adrenergic receptor antagonists, calcium channel blockers, fibrates, platelet aggregation inhibitors, HMG-CoA reductase inhibitors, and diuretics.

29. The method as recited in Claim 28 wherein the adrenergic receptor antagonist is chosen from atenolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, timolol, doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, tolazoline, bucindolol, carvedilol, and labetalol.
30. The method as recited in Claim 27 wherein the angiotensin II receptor antagonist is chosen from candesartan, eprosartan, irbesartan, losartan, olmesartan, tasosartan, telmisartan, valsartan, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate, molsidomin, and pentaerythritol tetranitrate.

31. The method as recited in Claim 27 wherein the angiotensin-converting enzyme inhibitor is chosen from captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, benazepril, cilazapril, fosinopril, trandolapril, spirapril, delapril, moexipril, temocapril, zofenopril, and imidapril.

32. The method as recited in Claim 27 wherein the anti-arrhythmic is chosen from quinidine, procainamide, disopyramide, sparteine, ajmaline, lidocaine, mexiletine, tocainide, aprindine, propafenone, flecainide, lorcanide, encainide, amiodarone, bretylium tosilate, bunaftine, dofetilide, ibutilide, moracizine, and cibenzoline.

33. The method as recited in Claim 27 wherein the anticoagulant is chosen from acenocoumarol, argatroban, bivalirudin, lepirudin, fondaparinux, heparin, phenindione, warfarin, and ximelagatran.

34. The method as recited in Claim 27 wherein the antiplatelet agent is chosen from abciximab, cilostazol, clopidogrel, dipyridamole, ticlopidine, and tirofibin.

35. The method as recited in Claim 27 wherein the beta-1 adrenergic receptor antagonist is chosen from betaxolol, alprenolol, oxprenolol, pindolol, propranolol, timolol, sotalol, nadolol, mepindolol, carteolol, tertatolol, bopindolol, bupranolol, enopropolol, cloranolol, practolol, metoprolol, atenolol, acebutolol, bevantolol, bisoprolol, celiprolol, esmolol, epanolol, s-atenolol, nebivolol, talinolol, labetalol, and carvedilol.

36. The method as recited in Claim 27 wherein the calcium channel blocker is chosen from amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, nilvadipine, manidipine, barnidipine, lercanidipine, cilnidipine, bendipine, mibefradil, verapamil, gallopamil, diltiazem, fendiline, bepridil, lidoflazine, and perhexiline.

37. The method as recited in Claim 27 wherein the fibrate is chosen from clofibrate, bezafibrate, aluminium clofibrate, gemfibrozil, fenofibrate, simfibrate, ronifibrate, ciprofibrate, etofibrate, and clofibrate.

38. The method as recited in Claim 27 wherein the platelet aggregation inhibitor is chosen from acetylsalicylic acid/aspirin, aloxiprin, ditazole, carbasalate calcium, cloricromen,
dipyridamole, indobufen, picotamide, triflusal, clopidogrel, ticlopidine, prasugrel, beraprost, prostacyclin, iloprost, and treprostinil.

39. The method as recited in Claim 27 wherein the HMG-CoA reductase inhibitor is chosen from atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

40. The method as recited in Claim 27 wherein the diuretic is chosen from bendroflumethiazide, hydroflumethiazide, hydrochlorothiazide, chlorothiazide, polythiazide, trichlormethiazide, cyclopenthiazide, methyclothiazide, cyclothiazide, mebutizide, quinethazone, clopamide, chlortalidone, mefruside, clofenamide, metolazone, meticrane, xipamide, indapamide, clorexolone, fenquizone, mersalyl, theobromine, cicletanine, furosemide, bumetanide, piretanide, torasemide, etacrynic acid, tienilic acid, muzolimine, etozolin, spironolactone, potassium canrenoate, canrenone, and eplerenone.

41. The method as recited in Claim 25, further resulting in at least one effect chosen from:
   a. decreased inter-individual variation in plasma levels of the compound or a metabolite thereof as compared to the non-isotopically enriched compound;
   b. increased average plasma levels of the compound per dosage unit thereof as compared to the non-isotopically enriched compound;
   c. decreased average plasma levels of at least one metabolite of the compound per dosage unit thereof as compared to the non-isotopically enriched compound;
   d. increased average plasma levels of at least one metabolite of the compound per dosage unit thereof as compared to the non-isotopically enriched compound; and
   e. an improved clinical effect during the treatment in the subject per dosage unit thereof as compared to the non-isotopically enriched compound.

42. The method as recited in Claim 25, further resulting in at least two effects chosen from:
   a. decreased inter-individual variation in plasma levels of the compound or a metabolite thereof as compared to the non-isotopically enriched compound;
   b. increased average plasma levels of the compound per dosage unit thereof as compared to the non-isotopically enriched compound;
   c. decreased average plasma levels of at least one metabolite of the compound per dosage unit thereof as compared to the non-isotopically enriched compound;
   d. increased average plasma levels of at least one metabolite of the compound
per dosage unit thereof as compared to the non-isotopically enriched compound; and

e. an improved clinical effect during the treatment in the subject per dosage unit thereof as compared to the non-isotopically enriched compound.

43. The method as recited in Claim 25, wherein the method effects a decreased metabolism of the compound per dosage unit thereof by at least one polymorphically-expressed cytochrome P450 isoform in the subject, as compared to the corresponding non-isotopically enriched compound.

44. The method as recited in Claim 43, wherein the cytochrome P450 isoform is chosen from CYP2C8, CYP2C9, CYP2C19, and CYP2D6.

45. The method as recited Claim 25, wherein the compound is characterized by decreased inhibition of at least one cytochrome P450 or monoamine oxidase isoform in the subject per dosage unit thereof as compared to the non-isotopically enriched compound.

46. The method as recited in Claim 45, wherein the cytochrome P450 or monoamine oxidase isoform is chosen from CYP1A1, CYP1A2, CYP1B1, CYP2a6, CYP2a13, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP2G1, CYP2J2, CYP2R1, CYP2S1, CYP3A4, CYP3A5, CYP3A5P1, CYP3A5P2, CYP3A7, CYP4A11, CYP4B1, CYP4F2, CYP4F3, CYP4F8, CYP4F11, CYP4F12, CYP4X1, CYP4Z1, CYP5A1, CYP7A1, CYP7B1, CYP8A1, CYP8B1, CYP11A1, CYP11B1, CYP11B2, CYP17, CYP19, CYP21, CYP24, CYP26A1, CYP26B1, CYP27A1, CYP27B1, CYP39, CYP46, CYP51, MAOA, and MAOB.

47. The method as recited in Claim 25, wherein the method reduces a deleterious change in a diagnostic hepatobiliary function endpoint, as compared to the corresponding non-isotopically enriched compound.

48. The method as recited in Claim 47, wherein the diagnostic hepatobiliary function endpoint is chosen from alanine aminotransferase ("ALT"), serum glutamic-pyruvic transaminase ("SGPT"), aspartate aminotransferase ("AST," "SGOT"), ALT/AST ratios, serum aldolase, alkaline phosphatase ("ALP"), ammonia levels, bilirubin, gamma-glutamyl transpeptidase ("GGT," "γ-GTP," "GTP"), leucine aminopeptidase ("LAP"), liver biopsy, liver ultrasonography, liver nuclear scan, 5'-nucleotidase, and blood protein.

49. A compound as recited in any one of Claims 1-23 for use as a medicament.

50. A compound as recited in any one of Claims 1-23 for use in the manufacture of a medicament for the prevention or treatment of a disorder ameliorated by the inhibition of 11-β-hydroxylase.