This invention relates to novel compounds that are substituted xanthine derivatives and pharmaceutically acceptable salts thereof. In particular, this invention relates to novel substituted xanthine derivatives that are derivatives of a pentoxifylline metabolite. This invention also provides compositions comprising one or more compounds of this invention and a carrier and the use of the disclosed compounds and compositions in methods of treating diseases and conditions for which pentoxifylline and related compounds are beneficial.

The compounds of the invention are represented by one of the following structural formulas:

\[
\text{CD3}
\]

wherein the values of \( R_1, R_2, Y_1 \) and \( Y_2 \) are described herein.

27 Claims, 6 Drawing Sheets
OTHER PUBLICATIONS


Honma et al., Drug Metab Dispos 15 (4): 551 (1987).*


Pieniaszek, et al., "Moricizine Bioavailability via Simultaneous, Dual Stable Isotope Administration: Bioequivalence Implications"


* cited by examiner
FIG. 1A
FIG. 1B
FIG. 2
* = not detected

FIG. 3
FIG. 4
FIG. 5
DEUTERIUM SUBSTITUTED XANTHINE DERIVATIVES

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 12/873,991, filed Sep. 1, 2010, and is a continuation-in-part of U.S. patent application Ser. No. 12/380,579, filed Feb. 27, 2009. This application claims the benefit of the priority of U.S. Provisional Application No. 61/239,342, filed Sep. 2, 2009. The contents of the foregoing applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Many current medicines suffer from poor absorption, distribution, metabolism and/or excretion (ADME) properties that prevent their wider use. Poor ADME properties are also a major reason for the failure of drug candidates in clinical trials. While formulation technologies and prodrug strategies can be employed in some cases to improve certain ADME properties, these approaches have failed to overcome the inherent ADME problems that exist for many drugs and drug candidates. One inherent problem is the rapid metabolism that causes a number of drugs, which otherwise would be highly effective in treating a disease, to be cleared too rapidly from the body. A possible solution to rapid drug clearance is frequent or high dosing to attain a sufficiently high plasma level of drug. This, however, introduces a number of potential treatment problems, such as poor patient compliance with the dosing regimen, side effects that become more acute with higher doses, and increased cost of treatment.

In some select cases, a metabolic inhibitor will be co-administered with an important drug that is rapidly cleared. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. These drugs are typically co-dosed with ritonavir, an inhibitor of cytochrome P450 enzyme CYP3A4, the enzyme responsible for their metabolism. Ritonavir itself has side effects and it adds to the pill burden for HIV patients who must already take a combination of different drugs. Similarly, dextromethorphan which undergoes rapid CYP2D6 metabolism is being tested in combination with the CYP2D6 inhibitor quinidine for the treatment of pseudobulbar disease.

In general, combining drugs with cytochrome P450 inhibitors is not a satisfactory strategy for decreasing drug clearance. The inhibition of a CYP enzyme activity can affect the metabolism and clearance of other drugs metabolized by that same enzyme. This can cause those other drugs to accumulate in the body to toxic levels.

A potentially attractive strategy, if it works, for improving a drug’s metabolic properties is deuterium modification. In this approach, one attempts to slow the CYP-mediated metabolism of a drug by replacing one or more hydrogen atoms with deuterium atoms. Deuterium is a safe, stable, non-radioactive isotope of hydrogen. Deuterium forms stronger bonds with carbon than hydrogen does. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and tolerability. At the same time, because the size and shape of deuterium are essentially identical to hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

Over the past 35 years, the effects of deuterium substitution on the rate of metabolism have been reported for a very small percentage of approved drugs (see, e.g., Blake, M I et al, J Pharm Sci, 1975, 64:637-91; Foster, A B, Adv Drug Res 1985, 14:1-40 (“Foster”); Kushner, D J et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, M B et al, Curr Opin Drug Discov Devel, 2006, 9:101-09 (“Fisher”)). The results have been variable and unpredictable. For some compounds deuterium causes decreased metabolic clearance in vivo. For others, there was no change in metabolism. Still others demonstrated decreased metabolic clearance. The variability in deuterium effects has also led experts to question or dismiss deuterium modification as a viable drug design strategy for inhibiting adverse metabolism. (See Foster at p. 35 and Fisher at p. 101).

SUMMARY OF THE INVENTION

This invention relates to novel compounds that are substituted xanthine derivatives and pharmaceutically acceptable salts thereof. For example, this invention relates to novel substituted xanthine derivatives that are structurally related to pentoxifylline. This invention also provides compositions comprising one or more compounds of this invention and a carrier and the use of the disclosed compounds and compositions in methods of treating diseases and conditions for which pentoxifylline and related compounds are beneficial.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. 1A and 1B depict the serum levels of a compound of this invention, pentoxifylline and certain of their respective metabolites in four individual dogs following oral administration of a combination of pentoxifylline and that compound of this invention.

FIG. 2 depicts the time course of the production of the specific metabolites measured in FIG. 3 following incubation of various compounds of this invention, pentoxifylline, (S)-M1 and (R)-M1 with rat whole blood.

FIG. 3 depicts the relative amount of specific metabolites produced following incubation of various compounds of this invention, pentoxifylline, (S)-M1 and (R)-M1 with rat whole blood.

FIG. 4 depicts the time course of the production of the specific metabolites measured in FIG. 5 following incubation of various compounds of this invention, pentoxifylline, (S)-M1 and (R)-M1 with human liver microsomes.

FIG. 5 depicts the relative amount of specific metabolites produced following incubation of various compounds of this invention, pentoxifylline, (S)-M1 and (R)-M1 with human liver microsomes.

DETAILED DESCRIPTION OF THE INVENTION

The terms “ameliorate” and “treat” are used interchangeably and include both therapeutic and prophylactic treatment. Both terms mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease...
the various synthesis steps used to prepare the compound.

“Disease” means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ. It will be recognized that some variation of natural isotopic abundance occurs in a synthesized compound depending upon the origin of chemical materials used in the synthesis. Thus, a preparation of pentoxifylline will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and inmaterial as compared to the degree of stable isotopic substitution of compounds of this invention. See, for instance, Wada E et al., Seikagaku, 1994, 66: 15; Ganesh L Z et al., Comp Biochem Physiol Mol Integr Physiol, 1998, 119: 725. In a compound of this invention, when a particular position is designated as having deuterium, it is understood that the abundance of deuterium at that position is substantially greater than the natural abundance of deuterium, which is 0.015%. A position designated as having deuterium typically has a minimum isotopic enrichment factor of at least 3340 (50.1% deuterium incorporation) at each atom designated as deuterium in said compound.

The term “isotopic enrichment factor” as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope.

In other embodiments, a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation) at each atom designated as deuterium in said compound.

In the compounds of this invention any atom not specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition. Also unless otherwise stated, when a position is designated specifically as “D” or “deuterium”, the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., at least 50.1% incorporation of deuterium).

The term “isotopologue” refers to a species that differs from a specific compound of this invention only in the isotopic composition thereof.

The term “compound,” when referring to a compound of this invention, refers to a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecule. Thus, it will be clear to those of skill in the art that a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure. The relative amount of such isotopologues in a compound of this invention will depend upon a number of factors including the isotopic purity of deuterated reagents used to make the compound and the efficiency of incorporation of deuterium in the various synthesis steps used to prepare the compound.

However, as set forth above, the relative amount of such isotopologues in toto will be less than 49.9% of the compound.

The invention also provides salts of the compounds of the invention. A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another embodiment, the compound is a pharmaceutically acceptable acid addition salt.

The term “pharmaceutically acceptable,” as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A “pharmaceutically acceptable salt” means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention. A “pharmaceutically acceptable counterion” is an ionic portion of a salt that is not toxic when released from the salt upon administration to a recipient.

Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen sulfide, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and phosphoric acid, as well as organic acids such as para-toluensulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, bensocid acid, fumaric acid, glutaric acid, gluconic acid, formic acid, glutamic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, lactic acid, oxalic acid, para-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid and acetic acid, as well as related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyrate, 1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthlate, sulfonate, xylene sulfonate, phenylacetate, phenylpropanoate, phenylbutyrate, citrate, lactate, β-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, napthalene-1-sulfonate, napthalene-2-sulfonate, mandelate and other salts. In one embodiment, pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

The invention also includes solvates and hydrates of the compound of the invention. As used herein, the term “hydrate” means a compound which further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces. As used herein, the term “solvate” means a compound which further includes a stoichiometric or non-stoichiometric amount of solvent such as water, acetone, ethanol, methanol, dichloromethane, 2-propanol, or the like, bound by non-covalent intermolecular forces.

It is understood that the carbon atom that bears substituents Y₁ and Y₂ in Formulae A, A₁, 1 and B can be chiral in some instances (when Y₁, Y₂ and R are different from one another) and in other instances it can be achiral (when at least two of Y₁, Y₂ and R are the same). This carbon atom (i.e., the carbon atom bearing Y₁ and Y₂) is indicated by an “*” in Formulae A,
A1, I and B. As such, chiral compounds of this invention can exist as either individual enantiomers, or as racemic or racemic mixtures of enantiomers. Accordingly, a compound of the present invention will include racemic and racemic enantiomeric mixtures, as well as individual respective stereoisomers that are substantially free from another possible stereoisomer. The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers, or less than "X"% of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are well known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

Unless otherwise indicated, when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

The term "stable compounds," as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or stororable intermediate compounds, treating a disease or condition responsive to therapeutic agents).


As used herein the term "alkylene" means a straight or branched chain divalent hydrocarbon radical, preferably having from one to six carbon atoms (C1-C6 alkylene). Examples of "alkylene" as used herein include, but are not limited to, methylene (CH2-), ethylene (—CH2CH2—), propylene (—CH2CH2CH2—), and branched versions thereof such as (—CH2CH2—), —CH2CH(—CH3)— and the like.

"Halogen" means chloro, bromo, fluoro, or iodo. "Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having 1 to 15 carbon atoms in the chain. Preferred alkyl groups have 1 to 12 carbon atoms in the chain, and more preferably 1 to 6 carbon atoms. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. Exemplary alkyl groups include methyl, methylene, difluoromethyl, trifluoromethyl, ethyl, cyclopentyilmethyl, cyclohexyilmethyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, n-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl; preferred are methyl, difluoromethyl and i-propyl. Alkyl groups may be optionally substituted with one or more groups selected from halo, cyano, oxo, amino, alkylamino, dialkylamino, cycloalkylcarbonyl, cycloalkylalkyl, aryalkyl, alkoxyalkyl, and alkylsilyl. Typically any alkyl or alkoxy moiety of the alkyl substituent group has 1 to 6 carbon atoms.

"Aryl" means an aromatic carbocyclic radical containing 6 to 10 carbon atoms. Exemplary aryl groups include phenyl or naphthyl. Aryl groups may be optionally substituted with one or more groups which may be the same or different, and which are selected from alkyl, aryl, alkoxy, aryloxy, alkoxyalkyl, halo, and nitro. Typically any alkyl or alkoxy moiety of the aryl substituent group has 1 to 6 carbon atoms.

"Heteroaryl" means a 5- to 10-membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the carbon atoms in the ring system is or are element(s) other than carbon, for example nitrogen, oxygen or sulfur. Heteroaryl groups may be optionally substituted with one or more groups which may be the same or different, and which are selected from alkyl, aryl, alkoxy, aryloxy, alkoxyalkyl, halo, and nitro. Exemplary heteroaryl groups include pyrazinyl, furanyl, thiophenyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, pyridazinyl, triazinyl, triazinyl, and quinolinyl.

"Alkylaryloxy" means an aryl-alkyl group in which the aryl and alkyl components are as previously described. Preferred alkylaryls contain a lower alkyl moiety. Exemplary alkylaryls include benzyl and 2-phenethyl.

"Heteroalkylaryloxy" means a heteroaryloxy group in which the heteroaryl and alkyl components are as previously described.

"Cycloalkyl" means a non-aromatic mono-, or multicyclic, or bridged ring system of 3 to 10 carbon atoms. The cycloalkyl group is optionally substituted by one or more halo, alkoxy, or a pharmaceutically acceptable salt thereof, where: R1 and R2 are each independently selected from hydrogen, —(C1-C4)alkyl, or —(C1-C4)alkylene-O—(C1-C4)alkyl, wherein the alkyl and alkoxy groups at each instance are independently and optionally substituted with deuterium; R3 is selected from —CH3, —CH2D, —CH2D2, and —CD3, R4 is n-butylene optionally substituted with deuterium;
R² is selected from hydrogen, deuterium, alkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, aryl, and heteroaryl, wherein each of the alkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, aryl, and heteroaryl is optionally substituted and wherein one or more hydrogen atoms in the alkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, heterocycloalkylalkyl, aryl, or heteroaryl or optional substituent thereof is optionally replaced with a corresponding number of deuterium atoms; and

either (a) Y¹ and Y² are each fluorine, or are taken together with the carbon to which they are bound to form C=O or (b) Y¹ is selected from fluorine and OH; and Y² is selected from hydrogen, deuterium, —CH₃, —CH₂D, —CHD₂ and —CD₃; with the provisos that:

- when Y¹ and Y² are taken together with the carbon to which they are bound to form C=O, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom; and
- when Y¹ is OH and Y² is hydrogen or CH₃, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom.

In another embodiment, the compound of Formula A is other than the following:

In a more specific aspect of this embodiment, at least one of Y¹ and Y² bears at least one deuterium atom.

In still another embodiment of Formula A, R¹ and R² are each methyl optionally substituted with deuterium; R³ is hydrogen or deuterium; and either: (a) Y¹ and Y² are taken together with the carbon atom to which they are bound to form C=O, or (b) Y¹ is —OH and Y² is selected from hydrogen and deuterium, with the provisos that:

- when Y¹ and Y² are taken together with the carbon to which they are bound to form C=O, then at least one of R₁, R₂, R³, R⁴, and R⁵ bears at least one deuterium atom; and
- when Y¹ is OH and Y² is hydrogen or CH₃, then at least one of R₁, R₂, R³, R⁴, and R⁵ bears at least one deuterium atom.

In another embodiment of Formula A, R⁵ is D, the compound having Formula A1:

In another embodiment of Formula A, when R¹ and R² are each methyl optionally substituted with deuterium and R³ is hydrogen or deuterium, then either: (i) Y¹ is fluorine; (ii) Y¹ is OH, and Y² is selected from —CH₃, —CH₂D, —CHD₂ and —CD₃; with the provisos that:

- when Y¹ and Y² are taken together with the carbon to which they are bound to form C=O, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom; and
- when Y¹ is OH and Y² is hydrogen or CH₃, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom.

In another embodiment, the compound of Formula A is other than the following:

In one aspect of Formula A1, R¹ and R² are each independently selected from —CH₃, —CH₂D, —CHD₂ and —CD₃; R³ is selected from —CH₃, —CH₂D, —CHD₂ and —CD₃; R⁴ is selected from —(CH₃)₄, —(CD₂)₄, —(CH₂)₆, and —(CD₂)₆; with the provisos that:

- when Y¹ and Y² are taken together with the carbon to which they are bound to form C=O, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom; and
- when Y¹ is OH and Y² is hydrogen or CH₃, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom.

In another aspect of Formula A1, R¹ and R² are each independently selected from —CH₃ and —CD₂; R³ is selected from —CH₃ and —CD₂; R⁴ is selected from —(CH₂)₄ and —(CD₂)₄; with the provisos that:

- when Y¹ and Y² are taken together with the carbon to which they are bound to form C=O, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom; and
- when Y¹ is OH and Y² is hydrogen or CH₃, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom.

In another embodiment of Formula A, when R¹ and R² are each methyl optionally substituted with deuterium and R³ is hydrogen or deuterium, then either: (i) Y¹ is fluorine; (ii) Y¹ is OH, and Y² is selected from —CH₃, —CH₂D, —CHD₂ and —CD₃; with the provisos that:

- when Y¹ and Y² are taken together with the carbon to which they are bound to form C=O, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom; and
- when Y¹ is OH and Y² is hydrogen or CH₃, then at least one of R₁, R₂, R₃, R⁴, and R⁵ bears at least one deuterium atom.

In another embodiment, the present invention provides a compound of Formula A, wherein R⁵ is hydrogen, the compound having Formula I:
wherein the alkyl and alkylene groups at each instance are independently and optionally substituted with deuterium;

R3 is selected from —CH3, —CH2D, —CHD2 and —CD3;
R4 is n-butylene optionally substituted with deuterium; and either (a) Y1 and Y2 are each fluorine, or taken together with the carbon to which they are attached, form C—O; or (b) Y1 is selected from fluorine and OH; and Y2 is selected from hydrogen, deuterium, —CH3, —CH2D, —CHD2 and —CD3, with the provisos that:

when Y1 and Y2 are taken together with the carbon to which they are attached to form C—O, at least one of R1, R2, R3 and R4 bears at least one deuterium atom; and

when Y1 is OH and Y2 is hydrogen or —CH3, then at least one of R1, R2, R3 and R4 bears at least one deuterium atom.

In a more specific embodiment of Formula I, R1 and R2 are each independently selected from —CH3, —CH2D, —CHD2 and —CD3; R3 is selected from —CH3, —CH2D, —CHD2 and —CD3; R4 is selected from —(CH2)6—, —(CD2)6—, —(CD2)5CH2— and —CD2(CH2)3—, wherein —“” represents the portion of the R4 moiety bound to C(Y1)(Y2) in the compound; and either: Y1 is OH and Y2 is selected from hydrogen and deuterium; or Y1 and Y2 are taken together with the carbon to which they are attached to form C—O.

In another aspect of Formula I, R1 and R2 are each independently selected from —CH3 and —CD3; R3 is selected from —CH3 and —CD3; R4 is selected from —(CH2)6— and —(CD2)6—; and either: Y1 is OH and Y2 is selected from hydrogen and deuterium; or Y1 and Y2 are taken together with the carbon to which they are attached to form C—O.

In another aspect of Formula I, R1 and R2 are each independently selected from —CH3 and —CD3; R3 is selected from —CH3 and —CD3; R4 is selected from —(CH2)6— and —(CD2)6—; and Y1 and Y2 are taken together with the carbon to which they are attached to form C—O.

In another embodiment, in any of the aspects set forth above, the compound of Formula I is other than the following:  

In yet another embodiment, in any of the aspects set forth above, the compound of Formula I is other than the following:

Another embodiment of the present invention provides a compound of Formula II:

or a salt thereof, wherein: 

R1 and R2 are each independently selected from hydrogen, —(C1–C4)alkyl, or —(C1–C4)alkylene-O—(C1–C4)alkyl, wherein the alkyl and alkylene groups at each instance are independently and optionally substituted with deuterium;
R3 is selected from —CH3, —CH2D, —CHD2 and —CD3; R4 is n-butylene optionally substituted with deuterium; and wherein at least one of R2, R3 and R4 bears at least one deuterium atom.

One embodiment relates to a compound of Formula A, A1, I, or II, wherein R2 and R3 are each independently selected from —CH3, —CH2D, —CHD2 and —CD3.
Another embodiment relates to a compound of Formula A, A1, I, or II, wherein R1, R2, and R3 are each independently selected from —CH3 and —CD3.

Another embodiment relates to a compound of Formula A, A1, I, or II, wherein R1 is selected from hydrogen, (C1-C4) alkyl, and (C1-C4) alkenylene-O(C1-C4) alky1.

Another embodiment relates to a compound of Formula A, A1, I, or II, wherein R2 is selected from hydrogen, (C1-C4) alkyl, and —C(=O)alkyl, wherein —CH2— represents the point where R2 is attached to C(Y1)(Y2) in the compound; and Y1 is fluoro; and Y2 is selected from deuterium, CH2, and (CD2)4-.

Another embodiment relates to a compound of Formula A, wherein R1 is selected from hydrogen, deuterium, alkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, and heterocycloalkyl, wherein each of alkyl, cycloalkyl, heterocycloalkyl, cycloalkylalkyl, and heterocycloalkylalkyl may be optionally substituted.

In other embodiments of Formula A, A1 or I:
a) each methylene unit in R4 is selected from —CH2— and —CD2—; more specifically R4 is selected from —(CH2)4—, —(CD2)4—, —CD2CH2CH2—, —CD2CD2CH2—, and —(CD2)3CH2—, wherein ““” represents the point where R4 is attached to C(Y1)(Y2) in the compound; b) when Y1 is F, Y2 is selected from hydrogen, —CH3, —CHD, —CD2, and —CD3; or c) when Y1 is F, Y2 is fluorine; or d) when Y1 and Y2 are not the same and Y2 is not the same and Y1 and R2 are not the same, the stereochemistry at ““” is represented by:

or e) when Y1 and Y2 are not the same and Y2 and R2 are not the same and Y1 and R2 are not the same, the stereochemistry at ““” is represented by:

In other embodiments of Formula A, A1 or I, R1 is —CD3; R2 and R3 are —CH3; Y1 and Y2 are taken together to form C—O; and R4 is selected from —(CH2)4—, —(CD2)4—, —CD2CH2CH2—, —CD2CD2CH2—, and —(CD2)3CH2—.

In other embodiments of Formula A, A1 or I, R1 is —CD3; R2 and R3 are —CH3; Y1 and Y2 are taken together to form C—O; and R4 is selected from —(CH2)4—, —(CD2)4—, —CD2CH2CH2—, —CD2CD2CH2—, and —(CD2)3CH2—.

In other embodiments of Formula A, A1 or I, R1 is —CD3; R2 and R3 are —CH3; R4 is —(CH2)4—; Y1 is fluorine; and Y2 is selected from deuterium, —CH3D, —CD2D, and —CD3D.

In other embodiments of Formula A, A1 or I, R1 is —CD3; R2 and R3 are —CH3; R4 is —(CH2)4—; R5 is deuterium; Y1 is fluorine, and Y2 is fluorine.

In other embodiments of Formula A or A1, R1 is —CD3; R2 and R3 are —CH3; R4 is —(CH2)4—; R5 is deuterium; Y1 is fluorine; and Y2 is fluorine.

In other embodiments of Formula A, A1 or I, Y1 is F; Y2 is selected from hydrogen; R1 is —CH3; and R4 is —(CH2)4—. In another embodiment, a compound of Formula B:

or a pharmaceutically acceptable salt thereof, wherein each of R1 and R2 is independently selected from —CH3 and —CD3; R1 is hydrogen or deuterium; each Z3 is hydrogen or deuterium; each Z4 is hydrogen or deuterium; and either (a) Y1 is OH, and Y2 is hydrogen or deuterium, or (b) Y1 and Y2 are taken together with the carbon to which they are attached to form C—O.

One embodiment provides a compound of Formula B, wherein each Z3, Z4, and Z5 is hydrogen. In one aspect, R1 and R2 are each —CD3. In another aspect R1 is deuterium. In another aspect, Y1 and Y2 are taken together with the carbon to which they are attached to form C—O. In another aspect Y1 is OH, and Y2 is hydrogen or deuterium.

Another embodiment provides a compound of Formula B, wherein each Z3, Z4, and Z5 is deuterium. In one aspect, R1 and R2 are each —CD3. In another aspect R1 is deuterium. In another aspect Y1 and Y2 are taken together with the carbon to which they are attached to form C—O. In another aspect Y1 is OH, and Y2 is hydrogen or deuterium.

Yet another embodiment provides a compound of Formula B, wherein R1 and R2 are each —CD3. In one aspect, R1 is deuterium. In another aspect each Z3, Z4, and Z5 is hydrogen and R1 is deuterium. In another aspect, each Z3, Z4, and Z5 is deuterium.

Another embodiment provides a compound of Formula B, wherein Y1 and Y2 are taken together with the carbon to which they are attached to form C—O. In one aspect, R1 is deuterium. In another aspect, each Z3, Z4, and Z5 is deuterium and R1 is deuterium.

A further embodiment provides a compound of Formula B, wherein Y1 and Y2 are taken together with the carbon to which they are attached to form C—O. In one aspect, R1 is deuterium. In another aspect each Z3, Z4, and Z5 is hydrogen and R1 is deuterium. In another aspect, each Z3, Z4, and Z5 is deuterium and R1 is deuterium.

A still further embodiment provides a compound of Formula B, wherein Y1 and Y2 are taken together with the carbon to which they are attached to form C—O. In one aspect, R1 is deuterium. In another aspect each Z3, Z4, and Z5 is hydrogen and R1 is deuterium. In another aspect, each Z3, Z4, and Z5 is deuterium and R1 is deuterium.
Another embodiment provides a compound of Formula B, wherein $R^2$ is deuterium.

Another embodiment provides a compound of Formula B, wherein $R^3$ is deuterium, $Z^1$, $Z^2$ and $Z^3$ is hydrogen and $R^1$ is deuterium.

Table 1 above shows examples of specific compounds of Formula 1. These examples are deuterated and/or fluorinated analogs of pentoxifylline and its metabolites.

Table 2 above shows examples of specific compounds of Formula 1 where $R^1$ is $H$ and $Y^2$ is $CH_3$ or $CD_3$. These compounds include deuterated and fluorinated analogs of Albiylfylline (HWA-138). Albiylfylline has been studied for uses that are associated with pentoxifylline.

Table 3 shows specific examples of Formula 1 where $R^1$ is $-CH_2-O-CH_2-CH_3$ optionally substituted with deuterium.
Table 3 above shows examples of specific compounds of Formula I where R¹ is —CH₂—O—CH₂CH₃, optionally substituted with deuterium. In these examples, Y¹ is OH or F and Y² is CH₃ or CD₂. These compounds include deuterated and fluorinated analogs of tofarolamine (HWA-448). Tofarolamine has been studied for the treatment of depression, urinary incontinence, irritable bowel syndrome and multiple sclerosis.

Table 4 above shows examples of specific compounds of Formula I where R¹ is —CH₂CH₂CH₃, optionally substituted with deuterium and Y¹ is OH or F.

Table 5 above shows examples of specific compounds of Formula I where R¹ is —CH₂CH₂CH₃, optionally substituted with deuterium and Y¹ and Y² are taken together as —O.
Table 5 above shows examples of specific compounds of Formula I where \( R^1 \) is \(-\text{CH}_2\text{CH}_2\text{CH}_3\) optionally substituted with deuterium and \( Y^1 \) and \( Y^2 \) are taken together as \(-\text{O} \). These compounds include deuterated analogs of propentofylline. Propentofylline has been studied for the treatment of Alzheimer’s disease, neuropathic pain, traumatic brain injury, dysuria, retinal or optic nerve head damage, and peptic ulcers. It has also been studied for controlling intracranial pressure, stabilization of auto-regulation of cerebral blood flow and inhibition of effects of allograft reaction.

### TABLE 6

Examples of Specific Compounds of Formula A, Deuterated and/or Fluorinated Analogs of Pentoxifylline and its Metabolites where \( R^5 \) is D

<table>
<thead>
<tr>
<th>Compound</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>( R^4 )</th>
<th>( R^5 )</th>
<th>( Y^1 )</th>
<th>( Y^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>CD3</td>
<td>CH3</td>
<td>CH3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
<td></td>
</tr>
<tr>
<td>401</td>
<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
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</tr>
<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
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</tr>
<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
<td></td>
</tr>
<tr>
<td>404</td>
<td>CH3</td>
<td>CH3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
<td></td>
</tr>
<tr>
<td>405</td>
<td>CD3</td>
<td>CH3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
<td></td>
</tr>
<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
<td></td>
</tr>
<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
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</tr>
<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
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<td>Taken together as (-\text{O} )</td>
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<tr>
<td>410</td>
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<td>CD3</td>
<td>CD3</td>
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<td>CD3</td>
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<td>CD3</td>
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<td>D</td>
<td>Taken together as (-\text{O} )</td>
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<tr>
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<td>CH3</td>
<td>CH3</td>
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<td></td>
</tr>
<tr>
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<td>CH3</td>
<td>CH3</td>
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<td>D</td>
<td>Taken together as (-\text{O} )</td>
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<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
<td></td>
</tr>
<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
<td></td>
</tr>
<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>Taken together as (-\text{O} )</td>
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</tr>
<tr>
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<td>CD3</td>
<td>CD3</td>
<td>CD3</td>
<td>D</td>
<td>OH</td>
<td>H</td>
</tr>
</tbody>
</table>

Table 6 above shows examples of specific compounds of Formula A. These examples are deuterated and/or fluorinated analogs of pentoxifylline and its metabolites where \( R^5 \) is deuterium.

In one aspect of the above embodiment, the compound is not any one of Compounds 100, 116, or 149.

Examples of specific compounds of this invention include the following:
The present invention provides a compound of Formula C:

or a pharmaceutically acceptable salt thereof, wherein R¹ is selected from —CH₃ and —CD₃; R² is selected from —CH₃ and —CD₃; one of Y¹ and Y² is —OH; and the other of Y¹ and Y² is deuterium or hydrogen.

provided that if R¹ is CD₃ and R² is CH₃, then Y² is —OH.

One embodiment provides a compound of Formula C, wherein R¹ is —CH₃.

One embodiment provides a compound of Formula C, wherein R¹ is —CD₃.

One embodiment provides a compound of Formula C, wherein R² is —CH₃.

One embodiment provides a compound of Formula C, wherein R² is —CD₃.

One embodiment provides a compound of Formula C, wherein R¹ is —CH₃ and R² is —CH₃. In one aspect of this embodiment, Y¹ is —OH. In another aspect, Y² is OH.

One embodiment provides a compound of Formula C, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:

In one aspect of this embodiment, Y¹ is deuterium. In another aspect, Y¹ is hydrogen.

One embodiment provides a compound of Formula C, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:
In one aspect of this embodiment, Y1 is deuterium. In another aspect, Y1 is hydrogen.

One embodiment provides a compound of Formula D, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:

In one aspect of this embodiment, Y2 is deuterium. In another aspect, Y2 is hydrogen.

Examples of the compounds of the formula D include the following compounds and pharmaceutically acceptable salts thereof:

or a pharmaceutically acceptable salt thereof, wherein R1 is selected from CH3 and CD3; R2 is selected from CH3 and CD3; one of Y1 and Y2 is —OH; and the other of Y1 and Y2 is deuterium or hydrogen;

with the proviso that

(i) if either one of Y1 and Y2 is deuterium, then R2 is CD3;

(ii) if either one of Y1 and Y2 is hydrogen, then R1 is CH3.

One embodiment provides a compound of Formula D, wherein R1 is —CH3.

One embodiment provides a compound of Formula D, wherein R1 is —CD3.

One embodiment provides a compound of Formula D, wherein R2 is —CH3.

One embodiment provides a compound of Formula D, wherein R2 is —CD3.

One embodiment provides a compound of Formula D, wherein R1 is —CH3 and R2 is —CH3. In one aspect of this embodiment, Y1 is —OH. In another aspect, Y2 is OH.

One embodiment provides a compound of Formula D, or a pharmaceutically acceptable salt thereof, wherein the compound has the structure:

In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance.

The synthesis of compounds of this invention can be achieved by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance in Sidzhakova, D et al., Farmatsiya, (Sofia, Bulgaria) 1988, 38(4): 1-5; Davis, P J et al., Xenobiotica, 1985, 15(12): 1001-10; Akgun, H et al., J Pharm Sci, 2001, 26(2): 67-71; German Patent publication DD 274334; Czech Patent Nos. CS
hydroxide in aqueous methanol may be employed to afford compounds (wherein X is chloro, bromide or iodide) in the presence of potassium carbonate or, invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure. Exemplary Synthesis

Methods for synthesizing compounds of Formula I are depicted in the following schemes.

**Scheme 1A. Synthesis of Compounds of Formula I**

$$\text{R}^3/\text{R}^4 - \text{N}/\text{TN}$$


Such methods can be carried out utilizing corresponding deuterated and optionally, other isotope-containing reagents and/or intermediates to synthesize the compounds delineated herein, or invoking standard synthetic protocols known in the art for introducing isotopic atoms to a chemical structure.

**Scheme 1B. Preparation of Compounds Where Y^1 = OH From Compounds of Formula II**

As depicted in Scheme 1B, compounds of Formula II can be used to make compounds where Y^1 is OH. Thus, compounds of Formula II are reduced with either sodium borohydride or sodium borodeuteride (commercially available at 99 atom % D) according to the general method of European Patent publication 0330031 to form compounds wherein Y^1 is OH and Y^2 is hydrogen or deuterium. The enantiomeric alcohol products may be separated, for example through the method of Nicklasson, Met al., Chirality, 2002, 14(8): 643-652. In an alternate method, enzymatic reduction affords an enantioselectively-enriched alcohol product using the methods disclosed in Pekala, E et al., Acta Poloniae Pharmaceutica, 2007, 64(2): 109-113, or in Pekala, E et al., Biotech J, 2007, 2(4): 492-496.

Stereoselective preparation of compounds where C(Y^1)(Y^2) is C(H)OH or C(D)OH from corresponding compounds where C(Y^1)(Y^2) is C(O) may be carried out in the presence of a ketoreductase or carbonyl reductase. Compounds of the invention where C(Y^1)(Y^2) is C(H)OH or C(D)OH may be prepared stereoselectively from corresponding compounds where C(Y^1)(Y^2) is C(O) by treating with a hydride source or a deuteride source in the presence of a ketoreductase or a deuteride reductase at an appropriate pH with an enantiomeric excess of at least 80%. The ketoreductase or carbonyl reductase that favors formation of a compound wherein the stereoisomer chemistry at the C(H)OH or C(D)OH group is (S) may be, for example, any one of ALMAC Carbonyl Reductases CRED A131, CRED A801, CRED A901, CRED A251, or CRED A271 (each commercially available from ALMAC Group Ltd, Craigavon, England), any one of CODEXIS Ketoreductases KRED-119, KRED-137, KRED-148, KRED-169, KRED-174, KRED-NADH 101, KRED-NADH 102, KRED-NADH 112, or KRED-NADH 126 (each commercially available from Codexis Inc., Redwood City, Calif.), or SYNCORE Ketoreductases ES-KRED-121, ES-KRED-128, ES-KRED-130, ES-KRED-142, ES-KRED-175, ES-KRED-169, or ES-KRED-171 (each commercially available from Syncore Labs, Shanghai, China). In one aspect of, the enzyme is selected from CRED A131, CRED A251, KRED-NADH 101, KRED-NADH 102, KRED-NADH 112, KRED-NADH 126, ES-KRED-121, ES-KRED-128, ES-KRED-130, ES-KRED-142, ES-KRED-169, or ES-KRED-171. In a more specific aspect, the enzyme is selected from CRED A131, CRED A251, and KRED-NADH 101. The ketoreductase or carbonyl reductase that favors formation of a compound wherein the stereochemistry at the C(H)OH or C(D)OH group is (R) may be, for example, any one of KRED-NADH-118, CRED A601-NADP, CRED A291-NADP, CRED A311-NADP, KRED-NAD-110, ES-KRED-120, ES-KRED-131, CRED A101-NADP.

The amount of ketoreductase or carbonyl reductase used in the reaction ranges from 0.05 wt % to 10 wt % as a percentage of the weight of the substrate, such as 0.5 wt % to 5 wt %. In one embodiment, the amount of enzyme is between 1.0 wt % and 2.0 wt %. In a more specific aspect, the amount of enzyme is about 1.0 wt %.

The hydride source is a compound or mixture that is capable of providing a hydride anion or a synthon of a hydride anion. The deuteride source is a compound or mixture that is capable of providing a deuteride anion or a synthon of a deuteride anion. A hydride or deuteride source comprises a catalytic co-factor and optionally, a co-factor regeneration system. A catalytic co-factor used with the ketone reductase or carbonyl reductase in the process of this invention is selected from NAD, NADP, NADH, NADPH, NAD2H and NADP2H. The choice of co-factor may be based upon (a) the presence or absence of a co-factor regeneration system; (b)
the requirement for a hydride versus a deuteride source; and (c) an appropriate pH to perform the method according to the present invention means buffer conditions that maintain the pH at between 6.0 and 7.5 throughout the reaction. In one embodiment, the pH of the reaction was maintained between 6.5 and 7.3. In another embodiment, the pH of the reaction was maintained between 6.0 and 7.0. Typically dropwise addition of KOH is used to maintain the desired pH because the enzymatic reaction generates acid. In one aspect, the pH of the reaction is maintained between 6.90 and 7.05. The process may be performed at a temperature of about 20°C to 37°C. In one aspect of this embodiment, the temperature is about 29°C to 32°C. The process may be performed over a time period of about 12 hours to about 24 hours. In one embodiment, the time period is about 24 hours to about 40 hours. In one embodiment, the time period is about 40 hours to about 72 hours. In one embodiment, the time period is a time period sufficient for less than about 5% of the initial amount of the compound wherein \( C(Y_1)(Y_2) \) is \( C\) to be present.

Synthesis of Compound 10

Referring to Scheme 1A, compounds that can be used as compound 10 to make compounds of Formula I are known and include, but are not limited to, the following: theobromine (wherein \( R_1 \) and \( R_2 \) are CH\(_3\)) which is commercially available. Isotopologues of 10 wherein: (a) \( R_1 \) is CD\(_3\) and \( R_2 \) is H\(_3\); (b) \( R_1 \) is H\(_3\) and \( R_2 \) is CD\(_3\); and (c) \( R_1 \) and \( R_2 \) are CD\(_3\) are all known. See Benchekroun, Yet al., J Chromatogr B, 1977, 688: 245; Ribon, Bet al., Coll INSERM, 1988, 164: 268; and Homing, M G et al., Proc Int Conf Stable Isot, 1976, 41-54. 3-Methyl-7-propylxanthine, wherein \( R_1 \) is n-propyl and \( R_2 \) is CH\(_3\), is commercially available. Compound 10 wherein \( R_1 \) is CH\(_2\)OCH\(_3\) and \( R_2 \) is CH\(_3\) is also known. See German patent application DE 3942872A1.

A synthesis of compound 10 is depicted in Scheme 2 starting with commercially-available N-nitroso-N-methylurea. Treatment with appropriately deuterated amine 12 in water affords N-alkylurea 13 following the methods of Boivin, J L et al., Canadian Journal of Chemistry, 1951, 29: 478-81. Urea 13 may be treated with 2-cyanoacetic acid and acetic anhydride to provide cyanoacetamide derivative 14, which is treated first with aqueous NaOH and then with aqueous HCl to provide cyclized pyrimidinedione 15 according to the methods of Dubey, P K et al., Indian Journal of Heterocyclic Chemistry, 2005, 14(4): 301-306. Alternatively, cyanoacetamide 14 may be treated with trimethylsilylchloride and hexamethyldisilazane to afford the cyclized product 15 via the methods of Fulle, F et al., Heterocycles, 2000, 53(2): 347-352.

Following the methods of Merlos, M et al., European Journal of Medicinal Chemistry, 1990, 25(8): 653-8, treatment of pyrimidinedione 15 with sodium nitrite in acetic acid, and then by ammonium hydroxide and sodium dithionite, yields purine derivative 17. Following the methods disclosed by Rybar, A et al., in Czech patent application CS 263595B1, alkylation of 17 with appropriately deuterated electrophile 18 (X is chloro, bromo, or iodo) in the presence of potassium carbonate and optionally in the presence of additives such as NaBr, KBr, NaI, KI, or iodine, affords compound 10.

Referring to Scheme 2, useful deuterated amine reagents 12 include, but are not limited to, commercially-available compounds such as n-propyl-d\(_7\)-amine, or known compounds such as 1-propan-1,1-d\(_2\)-amine (Moritz, F et al., Organic Mass Spectrometry, 1993, 28(3): 207-15). Useful deuterated urea reagents 13 may include, but are not limited to, commercially-available compounds such as N-methyl-d\(_3\)-urea.
Useful deuterated electrophiles 18 may include, but are not limited to, commercially-available compounds such as iodomethane-d₃, bromomethane-d₃, 1-bromopropane-d₇, or known compounds such as (chloromethoxy-d₂)-ethane (Williams, A G, WO 2002059070A1), or bromomethoxymethane-d₂ (Van der Veken, B J et al., Journal of Raman Spectroscopy, 1992, 23(4): 205-23), or (bromomethoxy-d₂)-methane-d₃ (Van der Veken, B J et al., Journal of Raman Spectroscopy, 1992, 23(4): 205-23. The commercially available deuterated intermediates 12, 13 and 18 mentioned above are available having an isotopic purity of at least 98 atom % D.

Synthesis of Intermediate 11a-d₅ (cf. Scheme 1A)

An approach to the preparation of compound 11a-d₅ (cf. Scheme 1A) (wherein R₃ is CD₃; R₄ is 1,1-d₂-CH₂(CH₂)₃—, and Y¹ and Y² are taken together to form =O), is depicted in Scheme 3. Thus, methyllithium is added to commercially-available delta-valerolactone 19 according to the procedure of Zhang, Q et al., Tetrahedron, 2006, 62(50): 11627-11634 to afford ketone 20. Treatment of 20 with TFA-d₁ (99 atom % D) in D₂O (99 atom % D) under microwave conditions provides deuterated ketone 21 according to the general method of Fodor-Csorba K, Tet Lett, 2002, 43: 3789-3792. The alcohol moiety in 21 is converted to the chloride upon treatment with triphenylphosphine and carbon tetrachloride to yield chloride 11a-d₅ following the general procedures of Clément, J-L, Org Biomol Chem, 2003, 1: 1591-1597.

Synthesis of Intermediates 11a-d₉ and 11a-d₁₁

1. LiAlH₄
2. POCl₃, pyr (or) PPh₃, NCS, CI₂Cl₂
3. D₂SO₄, D₂O, THF
Scheme 4 depicts a synthesis of compound 11a-d₉ and compound 11a-d₁₁. Thus, commercially-available 4-phenylbutyric acid 22 may be heated in D₂O (99 atom % D) in the presence of Pd/C and hydrogen gas to afford deuterated acid 23 according to the general methods of Esaki, et al., Chem Eur J, 2007, 13: 4052-4063. Addition of deuterated methylthiolium in the presence of trimethylsilyl chloride provides ketone 24, according to the general method of Porta, A et al., J Org Chem, 2005, 70(12): 4876-4878. Ketone 24 is converted to acetal 25 by treatment with D₂SO₄ (99 atom % D) and commercially-available ethyleneglycol-d₂ (99 atom % D). Treatment of 25 with NaIO₄ and RuCl₃ according to the general method of Gamier, J-M et al., Tetrahedron: Asymmetry, 2007, 18(12): 1434-1442 provides carboxylic acid 26. Reduction with either LiAlH₄ or LiAlD₄ (98 atom % D) provides the alcohols (not shown), which are then chlorinated using either phosphorus oxychloride or triphenylphosphine and N-chlorosuccinimide (Naidu, S Vet al., Tet Lett, 2007, 48(13): 2279-2282), followed by acetal cleavage with D₂SO₄ to provide chlorides 11a-d₉ and 11a-d₁₁, respectively.

Schemes 4a and 4b depict the synthesis of specific enantiomers of chlorides 11b-(R) (wherein Y¹ is fluorine; Y² is selected from hydrogen and deuterium; and the compound is in the (R) configuration) and 11b-(S) (wherein Y¹ is fluorine; Y² is selected from hydrogen and deuterium; and the compound is in the (S) configuration). In Scheme 4a, a deuterated (or nondeuterated) benzyl-protected alcohol 27, such as known [[(5R)-5-fluorohexyl]oxy]methyl]-benzene (PCT publication WO2000031003) is deprotected by hydrogenation in the presence of Pd/C to provide alcohol 28. The alcohol is chlorinated with thionyl chloride according to the general procedure of Lacan, G et al., J Label Compd Radiopharm, 2005, 48(9): 635-643 to afford chloride 11b-(R).

In Scheme 4b, a deuterated (or nondeuterated) alcohol 29, such as known (S)-(+)-5-fluorohexanol (Riswoko, A et al., Enantiomer, 2002, 7(1): 33-39) is chlorinated to afford chloride 11b-(S).

Scheme 5 depicts a synthesis of other intermediates 11c and 11e. Thus, following the methods of either Kutner, Andrzej et al., Journal of Organic Chemistry, 1988, 53(15): 3450-7, or of Larsen, S D et al., Journal of Medicinal Chemistry, 1994, 37(15): 2343-51, compounds 30 or 31 (wherein X is a halide) may be treated with deuterated Grignard reagent 32 to afford intermediate 11c wherein R³ and Y² are the same, Y¹ is OH, and X is a halide. Treatment with diethylaminosulfur trifluoride (DAST) in dichloromethane or toluene provides intermediate 11e wherein R³ and Y² are the same, Y¹ is F, and X is a halide according to the general procedures of either Karst, N A et al., Organic Letters, 2003, 5(25): 4839-4842, or of Kiso, M et al., Carbohydrate Research, 1988, 177: 51-67.

Commercially available halides can be used to make compounds 11a as disclosed in Scheme 5. For example, commercially-available 5-chlorovaleryl chloride, or commercially-available 5-bromovaleryl chloride, or commercially-available ethyl 5-bromovalerate, may be useful as reagents 30 or 31. Referring again to Scheme 5, use of commercially-available methyl-d₃-magnesium iodide as Grignard reagent 32 affords electrophile 11 wherein R³ and Y² are simultaneously CD₃.
alcohol 39, which is treated with either triphenylphosphine in CCl₄ (Sabitha, G et al., Tetrahedron Letters, 2006, (volume date 2007), 48(2): 313-315) or with methanesulfonyl chloride, lithium chloride, and 2,6-lutidine in DMF (Blaszykowski, C et al., Organic Letters, 2004, 6(21): 3771-3774) to afford chloride 40. Following the same methods as in Scheme 6, chloride 40 may be converted to 11e.

Scheme 7 depicts an alternate synthesis of intermediate 11e, wherein R³ and Y² are the same and X=Br. Thus, according to the procedures of Hester, J B et al., Journal of Medicinal Chemistry, 2001, 44(7): 1099-1115, commercially-available 4-chloro-1-butanol is protected via treatment with 3,4-dihydro-2H-pyran (DHP) and camphorsulfonic acid (CSA) to provide chloride 33. Generation of the corresponding Grignard reagent with magnesium, followed by addition of acetone (R³=Y²=CH₃) or acetone-d₆ (Y²=R³=CD₃), affords alcohol 34. Fluorination with diethylaminosulfur trifluoride (DAST) in CH₂Cl₂ provides fluoride 35. Deprotection with CSA in MeOH provides alcohol 36, and treatment with N-bromosuccinimide and triphenyl phosphine affords intermediate 11e.

Scheme 8 depicts a synthesis of intermediate 11e-d₈ wherein R³ and Y² are the same and X=Br. Thus, commercially-available THF-d₈ may be treated with DCI and ZnCl₂ according to the general methods of Yang, A et al., Huagong Shikan, 2002, 16(3): 37-39 to afford known chloride 42 (Alken, Rudolf-Giesbert, WO 2003080598A1). Following the same methods as in Scheme 6, chloride 42 may be converted to 11e-d₈.

Scheme 9 depicts the synthesis of intermediate 11e-d₈ wherein R³ and Y² are the same and X=Br. Thus, known carboxylic acid 43 (Lompa-Krzymien, L et al., Proc. Int. Conf. Stable Isot., 1976, Meeting Date 1975, 574-8) is treated with either diazomethane (according to the general method of Gamido, N Met al., Molecules, 2006, 11(6): 654-435-443) or with trimethylsilyl chloride and methanol-d₆, (according to the general method of Doussineau, T et al., Synlett, 2004, 10: 1735-1738) to provide methyl ester 44.

Scheme 6 depicts an alternate synthesis of intermediate 11e, wherein R³ and Y² are the same and X=Br. Thus, according to the procedures of Hester, J B et al., Journal of Medicinal Chemistry, 2001, 44(7): 1099-1115, commercially-available 4-chloro-1-butanol is protected via treatment with 3,4-dihydro-2H-pyran (DHP) and camphorsulfonic acid (CSA) to provide chloride 33. Generation of the corresponding Grignard reagent with magnesium, followed by addition of acetone (R³=Y²=CH₃) or acetone-d₆ (Y²=R³=CD₃), affords alcohol 34. Fluorination with diethylaminosulfur trifluoride (DAST) in CH₂Cl₂ provides fluoride 35. Deprotection with CSA in MeOH provides alcohol 36, and treatment with N-bromosuccinimide and triphenyl phosphine affords intermediate 11e.

Scheme 7 depicts the synthesis of intermediate 11e wherein R³ and Y² are the same and X=Br. Thus, commercially-available 4-hydroxy-butanoic acid ethyl ester 37 is treated with DHP and CSA, or with DHP, TsOH, pyridine, CH₂Cl₂ to provide ester 38. Reduction with LiAlD₄ affords deuterated alcohol 39, which is treated with either triphenylphosphine in CCl₄ (Sabitha, G et al., Tetrahedron Letters, 2006, (volume date 2007), 48(2): 313-315) or with methanesulfonyl chloride, lithium chloride, and 2,6-lutidine in DMF (Blaszykowski, C et al., Organic Letters, 2004, 6(21): 3771-3774) to afford chloride 40. Following the same methods as in Scheme 6, chloride 40 may be converted to 11e.
As in Scheme 5, treatment of the ester with deuterated Grignard reagent 45 affords intermediate 11c-ds. For example, use of commercially-available methyl-d3-magnesium iodide as Grignard reagent 45 affords 1lc-ds wherein R3 and Y2 are simultaneously CD3.

Scheme 11 depicts the synthesis of a compound of Formula A1. Thus, a compound of Formula I is treated with potassium carbonate in D2O to effect a hydrogen-to-deuterium exchange reaction, providing a compound of Formula A1. One skilled in the art will appreciate that additional hydrogen-to-deuterium exchange reactions may also occur elsewhere in the molecule.


An alternative synthesis of a compound of Formula A1 is depicted in Scheme 12. Thus, intermediate 10 (cf. Scheme 1A) is treated with potassium carbonate in D2O to effect a hydrogen-to-deuterium exchange reaction, providing compound 50 as either the N-D or N—H species. Alkylation with intermediate 11 in the presence of potassium carbonate affords compounds of Formula A1.
Scheme 12b. Alternative Synthesis of Compounds of Formula I.

An alternative synthesis of compounds of Formula I is depicted in Scheme 12b. Thus, compounds of Formula A1 are treated with potassium carbonate in water to effect a deuterium-to-hydrogen exchange, which affords other compounds of Formula I. Preferably, in the method of Scheme 12b, either (a) Y₁ and Y₂ are each fluorine; or (b) Y₁ is selected from fluorine and OH; and Y₂ is selected from hydrogen, deuterium, —CH₃, —CH₂D, —CHD₂ and —CD₃.

A number of novel intermediates can be used to prepare compounds of Formula A. Thus, the invention also provides such a compound which is selected from the following:
Compounds a-d above may be prepared as generally described in Org. Lett., 2005, 7: 1427-1429 using appropriately-deuterated starting materials. Compounds e-o may be prepared from the appropriate bromides listed above by reference to Scheme 15 shown below.

Certain xanthine intermediates useful for this invention are also novel. Thus, the invention provides a deuterated xanthine intermediate III:

where W is hydrogen or deuterium, and each of R\(^1\) and R\(^2\) is independently selected from hydrogen, deuterium, C\(_1\)-C\(_3\) alkyl optionally substituted with deuterium, and C\(_1\)-C\(_3\) alkoxyalkyl optionally substituted with deuterium. Examples of R\(^1\) and R\(^2\)C\(_1\)-C\(_3\) alkyl include —CH\(_3\), —CD\(_3\), —CH\(_2\)CH\(_2\)CH\(_3\), and —CD\(_2\)CD\(_2\)CD\(_3\). Examples of C\(_1\)-C\(_3\) alkoxyalkyl include —CH\(_2\)OCH\(_2\)CH\(_3\), —CD\(_2\)OCH\(_2\)CH\(_3\), —CD\(_2\)OCD\(_2\)CH\(_3\), and —CD\(_2\)OCD\(_2\)CD\(_3\).

Specific examples of formula III include the following:
Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

**Compositions**

The invention also provides pyrogen-free compositions comprising an effective amount of a compound of this invention or pharmaceutically acceptable salts thereof; and an acceptable carrier. Preferably, a composition of this invention is formulated for pharmaceutical use (“a pharmaceutical composition”), wherein the carrier is a pharmaceutically acceptable carrier. The carrier(s) are “acceptable” in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in an amount used in the medicament.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffers, substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as potassium chloride, sodium hydrogen carbonate, potassium hydrogen carbonate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, microcrystalline cellulose, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polypropylene-block polymers, polyethylene glycol and wool fat.

If required, the solubility and bioavailability of the compounds of the present invention in pharmaceutical compositions may be enhanced by methods well-known in the art. One method includes the use of lipid excipients in the formulation. See “Oral Lipid-Based Formulations: Enhancing the Bioavailability of Poorly Water-Soluble Drugs (Drugs and the Pharmaceutical Sciences),” David J. Hauss, ed. Informa Healthcare, 2007; and “Role of Lipid Excipients in Modifying Oral and Parenteral Drug Delivery: Basic Principles and Biological Examples,” Kishor M. Wasan, ed. Wiley-Interscience, 2006.

Another known method of enhancing bioavailability is the use of an amorphous form of a compound of this invention optionally formulated with a poloxamer, such as LUTROL™ and PLURONIC™ (BASF Corporation), or block copolymers of ethylene oxide and propylene oxide. See U.S. Pat. No. 7,014,866; and United States patent publications 20060094744 and 20060079502.

The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch or iontophoretic techniques). Other formulations may conveniently be presented in unit dosage form, e.g., tablets, sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington’s Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa. (17th ed. 1985).

Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active
ingredients with liquid carriers, liposomes or finely divided solid carriers, or both, and then, if necessary, shaping the product.

In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets each containing a predetermined amount of the active ingredient; a powder or granules; a solution or a suspension in an aqueous liquid or a non-aqueous liquid; an oil-in-water liquid emulsion; a water-in-oil liquid emulsion; packed in liposomes; or as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Compositions suitable for oral administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, 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. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane-diol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer’s solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions may be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, e.g.: Rabinowitz, J D and Zaffaroni, A C, U.S. Pat. No. 6,803,031, assigned to Alexza Molecular Delivery Corporation.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For topical application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petroleum, propylene glycol, polyoxethylene polyoxypropylene compound, emulsifying wax, and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldecanol, benzyl alcohol, and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

Thus, according to yet another embodiment, the compounds of this invention may be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents, or catheters. Suitable coatings and the general preparation of coated implantable devices are known in the art and are exemplified in U.S. Pat. Nos. 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials such as a hydrogel polymer, polymethylsiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings can optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition. Coatings for invasive devices are to be included within the definition of pharmaceutically acceptable carrier, adjuvant or vehicle, as those terms are used herein.

According to another embodiment, the invention provides a method of coating an implantable medical device comprising the step of contacting said device with the coating composition described above. It will be obvious to those skilled in the art that the coating of the device will occur prior to implantation into a mammal.

According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implant-
able drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

According to another embodiment, the invention provides an implantable drug release device impregnated with or containing a compound or a composition comprising a compound of this invention, such that said compound is released from said device and is therapeutically active.

Where an organ or tissue is accessible because of removal from the patient, such organ or tissue may be bathed in a medium containing a composition of this invention, a composition of this invention may be painted onto the organ, or a composition of this invention may be applied in any other convenient way.

In another embodiment, the compound of the invention comprises between 28 and 68% (w/w) of the composition. In this embodiment, magnesium stearate and microcrystalline cellulose comprise about 2% (w/w) of the composition.

In another embodiment, a composition of this invention further comprises a second therapeutic agent. The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as pentoxifylline. Such agents include those indicated as being useful in combination with pentoxifylline, including but not limited to, those described in WO 1997019868, EP 0640342, WO 2000313268, WO 2001032156, WO 2006035418, and WO 1996008388.

Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from peripheral obstructive vascular disease; glomerulonephritis; nephrotic syndrome; nonalcoholic steatohepatitis; Leishmaniasis; cirrhosis; liver failure; Duchenne’s muscular dystrophy; late radiation induced injuries; radiation induced lymphedema; radiation-associated necrosis; alcoholetic hepatitis; radiation-associated fibrosis; necrotizing enterocolitis in premature neonates; diabetic nephropathy, hypertension-induced renal failure, and other chronic kidney disease; Focal Segmental Glomerulosclerosis; pulmonary sarcoidosis; recurrent aphthous stomatitis; chronic breast pain in breast cancer patients; brain and central nervous system tumors; malnutrition-inflammation-cachexia syndrome; interleukin-1 mediated disease; graft versus host reaction and other allograft reactions; diet-induced fatty liver conditions, atherosomatic lesions, fatty liver degeneration and other diet-induced high fat or alcohol-induced tissue-degenerative conditions; human immunodeficiency virus type 1 (HIV-1) and other human retroviral infections; multiple sclerosis; cancer; fibroproliferative diseases; fungal infection; drug-induced nephrotoxicity; collagenous colitis and other diseases; and/or conditions characterized by elevated levels of platelet derived growth factor (PDGF) or other inflammatory cytokines; endometriosis; optic neuropathy and CNS impairments associated with acquired immunodeficiency syndrome (AIDS), immune disorder diseases, or multiple sclerosis; autoimmune disease; upper respiratory viral infection; depression; urinary incontinence; irritable bowel syndrome; septic shock; Alzheimers Dementia; neuropathic pain; dysuria; retinal or optic nerve damage; peptic ulcer; insulin-dependent diabetes; non-insulin-dependent diabetes; diabetic nephropathy; metabolic syndrome; obesity; insulin resistance; dyslipidemia; pathological glucose tolerance; hypertension; hyperlipidemia; hyperuricemia; gout; hypercoagulability; and inflammation or injury associated with neutrophil chemotaxis and/or degranulation. The compounds of this invention can also be used to control intraocular pressure or to stabilize auto-regulation of cerebral blood flow in subjects who require such control as determined by medical examination.

In one embodiment, the second therapeutic agent is selected from α-tocopherol and hydroxyurea.

In another embodiment, the second therapeutic agent is useful in the treatment of diabetes or an associated disorder, and is selected from insulin or insulin analogues, glucagon-like-peptide-1 (GLP-1) receptor agonists, sulfonylurea agents, biguanide agents, alpha-glucosidase inhibitors, PPAR agonists, meglitinide agents, dipetidyl-peptidase (DPP) IV inhibitors, other phosphodiesterase (PDE1, PDE5, PDE9, PDE10 or PDE11) inhibitors, amylin agonists, CoEnzyme A inhibitors, and antiobesity agents.

Specific examples of insulin include, but are not limited to Humulin® (human insulin, rDNA origin), Novolin®B (human insulin, rDNA origin), Velosulin®B IR (human buffered regular insulin, rDNA origin), Exubera® (human insulin, inhaled), and other forms of inhaled insulin, for instance, as delivered by Mannkind’s “Technosphere Insulin System”.

Specific examples of insulin analogues include, but are not limited to, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension and Lys-Pro insulin.

Specific examples of GlucaGon-Like-Peptide-1 receptor agonists include, but are not limited to BIM-51077 (CAS-No. 275371-94-3), EXENATIDE (CAS-No. 141758-74-9), CJC-1131 (CAS-No. 532951-64-7), LIAGLITAZIDE (CAS-No. 20656-20-2) and ZIP-10 (CAS-No. 320367-13-3).

Specific examples of sulfonylurea agents include, but are not limited to, TOLBUTAMIDE (CAS-No. 00064-77-7), TOLAZAMIDE (CAS-No. 00116-19-0), GLIPIZIDE (CAS-No. 029094-61-9), CARBUTAMIDE (CAS-No. 000339-43-5), GLISOXEPIDE (CAS-No. 025046-79-1), GLISENTIDE (CAS-No. 032797-92-5), GLIBORUNURIDE (CAS-No. 026944-48-9), GLIBENCAMIDE (CAS-No. 010238-21-8), GLIQUIDONE (CAS-No. 033342-05-1), GLIMEPIRIDE (CAS-No. 093479-97-1) and GLICLAZIDE (CAS-No. 021187-98-4).

A specific example of a biguanide agent includes, but is not limited to METFORMIN (CAS-No. 000657-24-9).

Specific examples of alpha-glucosidase-inhibitors include, but are not limited to ACARBOSE (CAS-No. 056180-94-0), MIGLITOL (CAS-No. 072432-03-2) and VOGLIBOSE (CAS-No. 083480-29-9).

Specific examples of PPAR-agonists include, but are not limited to MURAGLITAZAR (CAS-No. 351741-94-7), ROSIGLITAZONE (CAS-No. 122320-73-4), PIOGLITAZONE (CAS-No. 111025-46-8), RAGAGLITAZAR (CAS-No. 222834-30-2), FARGLITAZAR (CAS-No. 196808-45-4), TESAGLITAZAR (CAS-No. 251565-85-2), NAVeGLITAZAR (CAS-No. 476-436-68-7), NETOGLITAZONE (CAS-No. 161600-01-7), RIVeGLITAZONE (CAS-No. 185428-18-6), K-1 11 (CAS-No. 221564-97-2), GW-677954 (CAS-No. 622402-24-8), FK-614 (CAS-No. 193012-35-0) and (-)-Halofenate (CAS-No. 024136-23-0).

Preferred PPAR-agonists are ROSGILITAZONE and PIOGLITAZONE.

Specific examples of meglitinide agents include, but are not limited to REPAGLINIDE (CAS-No. 135062-02-1), NATEGLINIDE (CAS-No. 105816-04-4) and MITtGLINIDE (CAS-No. 145375-43-5).

Specific examples of DPP IV inhibitors include, but are not limited to SITAGLITIN (CAS-No. 486-46-3), SAXA-
A specific example of an amylase agonist includes, but is not limited to PRALISETINIDE (CAS-No. 151126-32-8).

A specific example of a Coenzyme A inhibitor includes, but is not limited to ETOMOXIR (CAS-No. 082258-36-4).

Examples of anti-obesity drugs include, but are not limited to HMR-1426 (CAS-No. 262376-75-0), CETILISTAT (CAS-No. 282526-98-1) and SIBUTRAMINE (CAS-No. 106650-56-0).

In another embodiment, the invention provides separate dosage forms of a compound of this invention and one or more of any of the above-described second therapeutic agents, wherein the compound and second therapeutic agent are associated with one another. The term “associated with one another” as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term “effective amount” refers to an amount which, when administered in a proper dosing regimen, is sufficient to treat (therapeutically or prophylactically) the target disorder. For example, and effective amount is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., Cancer Chemother. Rep, 1966, 50:219. Body surface area may be determined approximately from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

In one embodiment, an effective amount of a compound of this invention is in the range of 20 mg to 2000 mg per treatment. In more specific embodiments the amount is in the range of 40 mg to 1000 mg, or in the range of 100 mg to 800 mg, or more specifically in the range of 200 mg to 400 mg per treatment. Treatment typically is administered from one to three times daily.

Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician. For example, guidance for selecting an effective dose can be determined by reference to the prescribing information for pentoxifylline.

For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are incorporated herein by reference in their entirety.

It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

In one embodiment, the invention provides a method of inhibiting the activity of phosphodiesterase (PDE) in a cell, comprising contacting a cell with one or more compounds of Formula A, A1, I, II, B, C, or D.

In addition to its PDE inhibitory activity, pentoxifylline is known to suppress the production of a number of other biological agents such as interleukin-1 (IL-1), IL-6, IL-12, TNF-alpha, fibrinogen, and various growth factors. Accordingly, in another embodiment, the invention provides a method of suppressing the production of interleukin-1 (IL-1), IL-6, IL-12, TNF-alpha, fibrinogen, and various growth factors in a cell, comprising contacting a cell with one or more compounds of Formula A, A1, I, II, B, C, or D.

According to another embodiment, the invention provides a method of treating a disease in a patient in need thereof that is beneficially treated by pentoxifylline comprising the step of administering to said patient an effective amount of a compound of Formula A, A1, I, II, B, C, or D or a pharmaceutical composition comprising a compound of Formula A, A1, I, II, B, C, or D and a pharmaceutically acceptable carrier.

Such diseases are well known in the art and are disclosed in, but not limited to the following patents and published applications: WO 1988004928, EP 0493682, U.S. Pat. No. 5,112,827, EP 0484785, WO 1997019686, WO 2003013568, WO 2001032156, WO 1992007566, WO 1997051960, WO 1998055110, WO 2005023193, U.S. Pat. No. 4,975,432, WO 1993018770, WO 0490181, and WO 1996058586. Such diseases include, but are not limited to, peripheral obstructive vascular disease; glomerulonephritis; nephritic syndrome; nonalcoholic steatohepatitis; Leishmaniasis; cirrhosis; liver failure; Duchenne’s muscular dystrophy; late radiation induced injuries; radiation induced lymphedema; radiation-associated necrosis; alcoholic hepatitis; radiation-associated fibrosis; necrotizing enterocolitis in premature neonates; diabetic nephropathy, hypertension-induced renal failure, and other chronic kidney disease; Focal Segmental Glomerulosclerosis; pulmonary sarcoidosis; recurrent aphthous stomatitis; chronic breast pain in breast cancer patients; brain and central nervous system tumors; malnutrition-inflammation-cachexia syndrome; interleukin-1 mediated disease; graft versus host reaction and other allograft reactions; diet-induced fatty liver conditions, attherosomatic lesions, fatty liver degeneration and other diet-induced high fat or alcohol-induced tissue-degenerative conditions; human immunodeficiency virus type 1 (HIV-1) and other human retroviral infections, multiple scle-
radiation-associated necrosis, acute kidney failure or drug-induced nephrotoxicity; collagenous colitis and other diseases and/or conditions characterized by elevated levels of platelet derived growth factor (PDGF) or other inflammatory cytokines; endometriosis; optic neuropathy and CNS impairments associated with acquired immunodeficiency syndrome (AIDS), immune disorder diseases, or multiple sclerosis; autoimmune disease; upper respiratory viral infection; depression; urinary incontinence; irritable bowel syndrome; septic shock; Alzheimer's Dementia; neuropathic pain; dysuria; retinal or optic nerve damage; peptic ulcer; insulin-dependent diabetes; non-insulin-dependent diabetes; diabetic nephropathy; metabolic syndrome; obesity; insulin resistance; dyslipidemia; pathological glucose tolerance; hypertension; hyperlipidemia; hyperuricemia; gout; hypercoagulability; acute alcoholic hepatitis; olfaction disorders; patient ductus arterialis; chronic inflammatory bowel disease; blood vessels associated with neutrophil chemotaxis and/or degranulation.

The compounds of Formula A, A1, I, II, B, C, or D can also be used to control intravascular pressure or to stabilize auto-regulation of cerebral blood flow in subjects who require such control as determined by medical examination.

In one particular embodiment, the method of this invention is used to treat a disease or condition in a patient in need thereof selected from intermittent claudication on the basis of chronic occlusive arterial disease of the limbs and other peripheral obstructive vascular diseases; glomerulonephritis; Focal Segmental Glomerulosclerosis; nephrotic syndrome; nonalcoholic steatohepatitis; Leishmaniasis; cirrhosis; liver failure; Duchenne's muscular dystrophy; late radiation induced injuries; radiation induced lymphedema; alcoholic hepatitis; radiation-induced fibrosis; necrotizing enterocolitis in premature neonates; diabetic nephropathy, hypertension-induced renal failure and other chronic kidney diseases; pulmonary sarcoidosis; recurrent aphthous stomatitis; chronic breast pain in breast cancer patients; brain and central nervous system tumors; obesity; acute alcoholic hepatitis; olfaction disorders; endometriosis-associated infertility; malnutrition-inflammation-cachexia syndrome; and patent ductus arteriosus.

In one embodiment, the method of this invention is used to treat diabetic nephropathy, hypertensive nephropathy or intermittent claudication on the basis of chronic occlusive arterial disease of the limbs. In one specific aspect of this embodiment, the method of this invention is used to treat diabetic nephropathy.

In another particular embodiment, the method of this invention is used to treat a disease or condition in a patient in need thereof selected from intermittent claudication on the basis of chronic occlusive arterial disease of the limbs in one embodiment, the method of this invention is used to treat chronic kidney disease. The chronic kidney disease may be selected from glomerulonephritis, Focal Segmental Glomerulosclerosis, nephrotic syndrome, reflux uropathy, or polycystic kidney disease.

In one embodiment, the method of this invention is used to treat chronic disease of the liver. The chronic disease of the liver may be selected from nonalcoholic steatohepatitis, fatty liver degeneration or other diet-induced high fat or alcohol-induced tissue-degenerative conditions, cirrhosis, liver failure, or alcoholic hepatitis.

In one embodiment, the method of this invention is used to a diabetes-related disease or condition. This disease may be selected from insulin resistance, retinopathy, diabetic ulcers, radiation-associated necrosis, acute kidney failure or drug-induced nephrotoxicity.

In one embodiment, the method of this invention is used to treat a patient suffering from cystic fibrosis, including those patients suffering from chronic Pulmonary Bronchitis.

In one embodiment, the method of this invention is used to aid in wound healing. Examples of types of wounds that may be treated include venous ulcers, diabetic ulcers and pressure ulcers.

In another particular embodiment, the method of this invention is used to treat a disease or condition in a patient in need thereof selected from insulin dependent diabetes; non-insulin dependent diabetes; metabolic syndrome; obesity; insulin resistance; dyslipidemia; pathological glucose tolerance; hypertension; hyperlipidemia; hyperuricemia; gout; and hypercoagulability.

In one embodiment, the method of this invention is used to treat a disease or condition in a patient in need thereof wherein the disease or condition is selected from anemia, Graves disease, retinal vein occlusion, lupus nephritis, macular degeneration, myelodysplasia, pruritis of HIV origin, pulmonary hypertension, retinal artery occlusion, intestinal inflammation, ischemic optic neuropathy, acute pancreatitis, sickle cell anemia and beta thalassemia.

Methods delineated herein also include those wherein the patient is identified as in need of a particular stated treatment. Identifying a patient in need of such treatment can be in the judgment of a patient or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the patient one or more second therapeutic agents. The choice of second therapeutic agent may be made from any second therapeutic agent known to be useful for co-administration with pentoxifylline. The choice of second therapeutic agent is also dependent upon the particular disease or condition to be treated. Examples of second therapeutic agents that may be employed in the methods of this invention are those set forth above for use in combination compositions comprising a compound of this invention and a second therapeutic agent.

In particular, the combination therapies of this invention include co-administering a compound of Formula A, A1, I, II, B, C, or D and a second therapeutic agent for treatment of insulin resistance; dyslipidemia; hyperuricemia; gout; and hypercoagulability.

The combination therapies of this invention also include co-administering a compound of Formula A, A1, I, II, B, C, or D and a second therapeutic agent for treatment of insulin dependent diabetes; non-insulin dependent diabetes; metabolic syndrome; obesity; insulin resistance; dyslipidemia; pathological glucose tolerance; hypertension; hyperlipidemia; hyperuricemia; gout; and hypercoagulability.

The term “co-administered” as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form
(such as a composition of this invention comprising a compound of the invention and a second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a patient does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said patient at another time during a course of treatment.

Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan’s purview to determine the second therapeutic agent’s optimal effective-amount range.

In one embodiment of the invention, where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

In yet another aspect, the invention provides the use of a compound of Formula A, A1, I, II, B, C, or D alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a patient of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula A, A1, I, II, B, C, or D for use in the treatment or prevention in a patient of a disease, disorder or symptom thereof delineated herein.

SYNTHETIC EXAMPLES

The synthetic examples below provide detailed procedures for making certain compounds of this invention. It will be apparent to one skilled in the art that further compounds of this invention may be prepared through the use of other reagents or intermediates by reference to these procedures and the schemes described above. The prepared compounds were analyzed by NMR, mass spectrometry, and/or elemental analysis as indicated. 1H NMR were taken on a 300 MHz instrument, which was useful for determining deuterium incorporation. Unless otherwise stated, the absence of an NMR signal as noted in the examples below indicates a level of deuterium incorporation that is at least 90%.

**Example 1**

Synthesis of 3-Methyl-7-(methyl-d3)-1H-purine-2,6,9(3H,7H)-dione (Compound 100)

**Scheme 13. Preparation of Compounds 100 and 409.**

**Step 1.** 3-Methyl-7-(methyl-d3)-1H-purine-2,6,9(3H,7H)-dione (51). A suspension of 3-methylxanthine 50 (5.0 g, 30.1 mmol, 1 equiv) and powdered K2CO3 (5.0 g, 36.0 mmol, 1.2 equiv) in DMF (95 mL) was heated to 60°C. Iodomethane-d3 (Cambridge Isotopes, 99.5 atom % D, 25.5 mL, 36.0 mmol, 1.2 equiv) was added via syringe. The resulting mixture was heated at 80°C for 5 hours (h). The reaction mixture was cooled to room temperature (rt) and the DMF was evaporated under reduced pressure. The crude residue was dissolved in 5% aqueous NaOH (50 mL), resulting in a dull yellow solution. The aqueous solution was washed with CH2Cl2 three times (500 mL total). The aqueous layer was acidified to pH 5 with acetic acid (6 mL), resulting in formation of a tan precipitate. The mixture was cooled in an ice-water bath, and the solids were filtered and washed with cold water. The solid was dried in a vacuum oven to give 2.9 g of 51 as a tan solid. The filtrate was concentrated to approxi-
mately 25 mL and a second crop (0.70 g) of 51 was collected by filtration. The total yield of 51 was 3.6 g. The crude material was used without further purification.

Step 2. 3-Methyl-7-(methyl-d3)-1-(5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (Compound 100). Crude 51 (1.50 g, 8.2 mmol, 1 equiv) and powdered K2CO3 (2.28 g, 16.4 mmol, 2 equiv) were suspended in DMF (50 mL) and heated to 50° C. To the resulting tan suspension was added 6-chloro-2-hexanone (52, 1.2 mL, 9.0 mmol, 1.1 equiv) and the reaction temperature was raised to 130° C. Heating was continued at 130° C for 2 h, during which time the suspension became finer and darker in color. The reaction mixture was cooled to rt and DMF was evaporated under reduced pressure. The residual tan paste was suspended in EtOAc (250 mL) and filtered to remove insoluble material. The filtrate was concentrated under reduced pressure resulting in a yellow oil. The crude product was purified using an Analogix chromatography system eluting with 100% EtOAc (10 minutes) followed by a gradient of 0 to 25% MeOH/EtOAc over 50 minutes (min). Product fractions were concentrated under reduced pressure to give a slightly yellow oil that solidified after standing for several minutes. The solid was triturated with heptanes (100 mL) and filtered to give 2.00 g of 100 as an off-white solid. mp 101.8-103.0° C. 1H-NMR (300 MHz, CDC13): δ 1.64-1.68 (m, 4H), 2.15 (s, 3H), 2.51 (t, J=7.0, 2H), 3.57 (s, 3H), 4.01 (t, J=7.0, 2H), 7.52 (s, 1H). 3.57 (s, 3H), 4.01 (t, J=7.0, 2H).

The Table below shows an exemplary deuteration on three separate batches of a compound having a CH3C(O)CH2 functional group in 100 to the CD3C(O)CD2 functional group in 409 may be generally applied under analogous conditions to convert compounds having one or more hydrogens alpha to the carbonyl group to compounds having one or more deuteriums in place of the corresponding one or more hydrogens. In one embodiment, successive H/D exchange reactions may be performed as needed to further increase the amount of deuterium incorporation. In one aspect of this embodiment, any excess D2O at the end of a second H/D exchange reaction in a given batch run may be used in a first H/D exchange reaction in a subsequent batch run; and any excess D2O at the end of a third H/D exchange reaction in a given batch run may be used in a second H/D exchange reaction in a subsequent batch run.

The Table below shows an exemplary deuteration on three separate batches of a compound having a CH3C(O)CH2 functional group and indicates the deuteration agent (either >99% D2O or an aqueous phase obtained from a later deuteration cycle of another batch) that may be used according to this invention.

Example 2

Synthesis of 8-d1,-3-methyl-7-(methyl-d3)-1-(6-d1-4-d2-5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (Compound 409)

8-d1,-3-methyl-7-(methyl-d3)-1-(6-d1-4-d2-5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (Compound 409). A suspension of 100 (1.80 g, 6.4 mmol, 1 equiv) and powdered K2CO3 (0.23 g, 1.7 mmol, 0.25 equiv) in D2O (Cambridge Isotope Labs, 99 atom % D) (45 mL) was stirred under reflux conditions for 24 h during which time the suspension became a slightly yellow solution. The reaction mixture was cooled to rt, saturated with sodium chloride, and extracted four times with dichloromethane (400 mL total). The combined organic phase was dried over Na2SO4, filtered, and evaporated under reduced pressure to provide 1.7 g of a slightly yellow oil that solidified upon standing. The crude material was re-subjected to the hydrogen/deuterium exchange conditions described above with fresh K2CO3 and D2O. After an identical workup, the off-white solid was triturated with hexanes (100 mL) and filtered to give 1.61 g of 409 as an off-white solid, mp 99.6-99.8° C. 1H-NMR (300 MHz, CDC13): δ 1.64-1.69 (m, 4H), 3.57 (s, 3H), 4.01 (t, J=7.0, 2H). 13C-NMR (75 MHz, CDC13): δ 21.05, 27.61, 29.90, 41.02, 107.83, 148.99, 151.69, 155.50, 209.28. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN; Wavelength: 254 nm): retention time: 3.29 min; 98% purity. MS (M+H): 298.3. Elemental Analysis (C13H15D3N4O3): Calculated: C 55.50, H 6.45, N 19.92. Found: C=55.58, H=6.48, N=19.92. 2.1x50 mm 3 μm C18-RP column—gradient method 5-95%
By way of example, the conversion of pentoxifylline may be effected in successive batches. The following table shows the percentage of deuterium incorporation at each of the methyl(CO), (CO)methylene, and the imidazole ring methine carbon for successive batch runs of 50 kg of pentoxifylline in each batch:

<table>
<thead>
<tr>
<th>Batch</th>
<th>Exchange 1</th>
<th>Exchange 2</th>
<th>Exchange 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>methyl(CO)</td>
<td>methyl(CO)</td>
<td>methine</td>
</tr>
<tr>
<td>Batch 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>88.6</td>
<td>88.8</td>
<td>13.8</td>
</tr>
<tr>
<td></td>
<td>97.8</td>
<td>98.0</td>
<td>26.3</td>
</tr>
<tr>
<td></td>
<td>99.2</td>
<td>99.2</td>
<td>37.4</td>
</tr>
<tr>
<td>Batch 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>82.3</td>
<td>83.8</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>96.7</td>
<td>96.8</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td>98.9</td>
<td>98.9</td>
<td>26.4</td>
</tr>
<tr>
<td>Batch 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>78.0</td>
<td>80.8</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td>95.1</td>
<td>95.6</td>
<td>11.6</td>
</tr>
<tr>
<td></td>
<td>98.9</td>
<td>99.0</td>
<td>27.1</td>
</tr>
<tr>
<td></td>
<td>99.3</td>
<td>99.4</td>
<td>32.6</td>
</tr>
</tbody>
</table>

RI-2: recycled from Batch 1, Exchange 2
RI-3: recycled from Batch 1, Exchange 3
R2-2: recycled from Batch 2, Exchange 2
R2-3: recycled from Batch 2, Exchange 3

Step 1. Synthesis of 3,7-Di(methyl-d3)-1-(5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (Compound 101)
tolylene (60 mL) and CD3,1 (4 mL, Cambridge Isotopes, 99.5 atom % D). The reaction mixture was heated in a 120°C oil bath and stirred for 24 hours, during which time the reaction mixture turned yellow and a solid formed. The reaction mixture was cooled to room temperature, resulting in the entire reaction mixture solidifying to a yellow solid. The mixture was diluted with acetone (30 mL) and MeOH (5 mL) and filtered under a stream of N2. The solids were washed with acetone (100 mL) which removed the yellow color to afford an off-white solid. The solid was dried on the filter under a stream of N2 to give a mixture of 55 and monoalkylated side product, 7-(methyl-d3)-xanthine in a roughly 1:1 ratio. Total mass recovery was 2.6 g (42% crude yield). Due to the poor solubility of this mixture, it was carried forward without further purification.

Step 2. 3,7-Di(methyl-d3)-1-(5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (Compound 101). A suspension of crude 55 (2.50 g, 13.4 mmol, 1.0 equiv) and powdered K2CO3 (2.20 g, 16 mmol, 1.2 equiv) in DMF (50 mL) was heated to 100°C. To the resulting tan suspension was added 6-chloro-2-hexanone (2.90 g, 14.8 mmol, 1.1 equiv) and the mixture was heated to 140°C. Heating was continued at 140°C for 4 hours during which time the suspension became finer and darker in color. The reaction mixture was cooled to room temperature and the DMF was evaporated under reduced pressure. The resulting tan paste was suspended in 1:1 dichloromethane/ethyl acetate (200 mL) and filtered to remove insoluble material. The filtrate was concentrated under reduced pressure giving a yellowish-brown oil (3.0 g). This crude reaction product was adsorbed onto silica gel and dried-loaded onto a silica gel column packed with 100% dichloromethane. The filtrate was concentrated under reduced pressure to afford a yellow oil (3.0 g). This crude reaction product was re-subjected to the above reaction conditions with fresh powdered K2CO3 and D2O. After an identical workup, the off-white solid was triturated with hexanes (50 mL) and filtered to give 0.45 g (74%) of Compound 413 as an off-white solid, mp 99.2-99.3°C. 1H-NMR (300 MHz, CDCl3): δ 1.64-1.71 (m, 4H), 4.01 (t, J=7.0, 2H), 5.21 (2.50 g, 2.15 mmol). Calculated: C 53.78, H 6.25, N 19.30. Found: C=53.76, H=6.39, N=19.11.

Notable in the 1H-NMR spectrum above was the absence of the following peaks: a singlet at around 2.15 ppm indicating the presence of cyclohexene hydrogens; a singlet around 3.57 ppm indicating an absence of methyl ketone hydrogens; a triplet at around 4.01 ppm in the above H-NMR spectrum above was the absence of hydrogens on the N-methyl group at the 7 position on the purine ring. Due to the poor solubility of this mixture, it was carried forward without further purification.

Example 4

Synthesis of 3-Methyl-7-(methyl-d3)-1-(6,6,6-d3-5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (Compound 99)

Scheme 15. Preparation of Compound 99.

Example 5

Synthesis of 3-Methyl-7-(methyl-d3)-1-(4,4,6,6,6-d5-5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (Compound 413)
Step 1. 5-(3-Methyl-7-(methyl-d3)-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methoxy-N-methylpentanamide (57). A suspension of 51 (1.50 g, 8.2 mmol, 1.0 equiv, see Example 1 for preparation) and powdered K₂CO₃ (1.80 g, 12.9 mmol, 1.6 equiv) in DMF (40 mL) was heated to 60° C. 5-Bromo-N-methoxy-N-methylpentanamide 56 (2.21 g, 9.8 mmol, 1.2 equiv, prepared as outlined in Org. Lett., 2005, 7: 1427-1429) was added and the mixture was heated at 110° C for 4 hours during which time the suspended solid became finer and tan in color. The reaction mixture was cooled to room temperature and DMF was evaporated under reduced pressure. The resulting tan paste was suspended in 1:1 CH₂Cl₂-ethyl acetate (250 mL) and the suspension was filtered to remove insoluble material. The filtrate was concentrated under reduced pressure to a slightly yellow oil. 1H-NMR of the oil indicated it contained approximately 10% unreacted 51. A second purification on an Analogix automated chromatography system eluting with 100% CH₂Cl₂ for 10 minutes followed by a gradient of 0-5% MeOH/CH₂Cl₂ over 40 minutes. The desired product elutes at approximately 24 minutes. Fractions containing product were concentrated under reduced pressure to a slightly yellow oil. ¹H NMR of the oil indicated it contained approximately 10% unreacted 51. A second purification on an Analogix automated chromatography system eluting with 100% CH₂Cl₂ for 10 minutes followed by a gradient of 0-5% MeOH/CH₂Cl₂ over 50 minutes allowed for removal of the impurity. Fractions containing product were concentrated under reduced pressure to a slightly yellow oil that crystalized as an off-white solid on standing. The solid was triturated with heptanes (100 mL) and filtered to give 1.29 g (49%) of 57 as a white solid. mp 93.7-94.4° C. Fractions containing unreacted starting material were also collected and concentrated to give 0.21 g of 57 as a clear, colorless oil. The recovered material was re-subjected to the above alkylation reaction to give, after workup and purification, an additional 0.06 g (33%, 62% overall based on total starting material) of Compound 99 as a white solid, mp 93.7-94.4° C. Fractions containing unreacted starting material were also collected and concentrated to give 0.06 g (33%, 32% overall based on total starting material) of 57 as an off-white solid. mp 93.7-94.4° C.

Notable in the ¹H-NMR spectrum above was the absence of a singlet at around 3.15 ppm indicating an absence of methyl ketone hydrogens. Due to the presence of a triplet at 4.01 ppm in the above ¹H-NMR spectrum, determination of the presence or absence of a singlet peak at around 3.99 ppm corresponding to the presence or absence of hydrogens on the N-methyl group at the 7 position (R₁) of the purine ring was not possible.

**Example 6**

**Synthesis of (α)-8-d₁-1-(4,4,6,6-d₅-5-Hydroxyhexyl)-3-methyl-7-(methyl-d₃)-1H-purine-2,6(3H,7H)-dione (Compound 419)**

**Scheme 16. Preparation of Compounds 419, 419(R), and 419(S).**
(+)-8-d1-1-(4,4,6,6,6-d5-5-Hydroxyhexyl)-3-methyl-7-(methyl-d3)-1H-purine-2,6(3H,7H)-dione (Compound 419). Compound 409 (0.50 g, 1.7 mmol, 1.0 equiv, see Example 2) was dissolved in EtOD (13 mL, Aldrich 99.5 atom % D) and NaBH4 (0.07 g, 1.9 mmol, 1.1 equiv) was added. An increase in temperature from 24 to 28°C was observed. The reaction was stirred 2 hours at room temperature, then was quenched by the addition of D2O (30 mL, Cambridge Isotope Labs, 99 atom % D). The crude product was purified by silica gel chromatography eluting first with 1% MeOH/CH2Cl2 followed by a gradient of 1-5% MeOH/CH2Cl2. Fractions containing product were concentrated under reduced pressure to give 0.16 g each of 419(R) (mp 107.8-108.8°C) and 419(S) (mp 108.3-108.4°C) as off-white solids.

A. (R)-8-d1-1-(4,4,6,6,6-d5-5-Hydroxyhexyl)-3-methyl-7-(methyl-d3)-1H-purine-2,6(3H,7H)-dione (Compound 419(R)). 1H-NMR (300 MHz, CDCl3): δ 1.36-1.50 (m, 2H), 1.60-1.74 (m, 3H), 3.14 (s, 3H), 3.80 (s, 1H), 4.02 (t, J=7.3, 2H). 13C-NMR (75 MHz, CDCl3): δ 22.70, 27.86, 29.71, 41.14, 67.66, 107.66, 148.78, 151.54, 155.40. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 tm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 254 nm): retention time: 3.26 min; 99.9% purity. Chiral HPLC (method: CHIRALPAK® AD 25 cm column—isonicotinic acid method 78% hexane/22% isopropanol/0.01% diethyamine for 40 min at 1.00 mL/min; Wavelength: 254 nm): retention time: 27.51 min (major enantiomer); 31.19 min (expected for minor enantiomer); >99.9% ee purity. MS (M+H): 290.1. (M+Na): 312.3. Elemental Analysis (C13H13D2N3O2): Calculated: C 53.97, H 6.97, N 19.36. Found: C=54.39, H=7.11, N=18.98.

Notable in the 1H-NMR spectrum above was the absence of the following peaks: a peak at around 1.19 ppm indicating an absence of methyl hydrogens alpha to the hydroxyl group; and a singlet at around 7.51 ppm indicating an absence of hydrogen at the number 8 position on the purine ring. Due to the presence of a multiplet at 1.36-1.50 ppm and a triplet at 2.01 ppm in the above 1H-NMR spectrum, determination of the presence or absence a peak at 1.51 ppm corresponding to the presence or absence of methylene hydrogens alpha to the hydroxyl group and of a singlet peak at around 3.95 ppm corresponding to the presence or absence of hydrogens on the N-methyl group at the 7 position (R) of the purine ring was not possible.

B. (S)-8-d1-1-(4,4,6,6,6-d5-5-Hydroxyhexyl)-3-methyl-7-(methyl-d3)-1H-purine-2,6(3H,7H)-dione (Compound 419(S)). 1H-NMR (300 MHz, CDCl3): δ 1.41-1.48 (m, 2H), 1.64-1.72 (m, 3H), 3.14 (s, 3H), 3.79 (s, 1H), 4.02 (t, J=7.4, 2H). 13C-NMR (75 MHz, CDCl3): δ 22.70, 27.86, 29.71, 41.15, 67.66, 107.67, 148.78, 151.54, 155.41. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 tm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 254 nm): retention time: 3.26 min; 99.9% purity. Chiral HPLC (method: CHIRALPAK® AD 25 cm column—isonicotinic acid method 78% hexane/22% isopropanol/0.01% diethyamine for 40 min at 1.00 mL/min; Wavelength: 254 nm): retention time: 27.51 min (major enantiomer); 31.19 min (expected for minor enantiomer); >99.9% ee purity. MS (M+H): 290.1. (M+Na): 312.3. Elemental Analysis (C13H13D2N3O2): Calculated: C 53.97, H 6.97, N 19.36. Found: C=54.35, H=7.28, N=18.75.

Notable in the 1H-NMR spectrum above was the absence of the following peaks: a peak at around 1.19 ppm indicating an absence of methyl hydrogens alpha to the hydroxyl group; and a singlet at around 7.51 ppm indicating an absence of hydrogen at the number 8 position on the purine ring. Due to the presence of a multiplet at 1.36-1.50 ppm and a triplet at 2.01 ppm in the above 1H-NMR spectrum, determination of the presence or absence a peak at 1.51 ppm corresponding to the presence or absence of methylene hydrogens alpha to the hydroxyl group and of a singlet peak at around 3.95 ppm corresponding to the presence or absence of hydrogens on the N-methyl group at the 7 position (R) of the purine ring was not possible.

Example 7

Chiral Separation of (R)-8-d1-1-(4,4,6,6,6-d5-5-Hydroxyhexyl)-3-methyl-7-(methyl-d3)-1H-purine-2,6(3H,7H)-dione (Compound 419(R)) and (S)-8-d1-1-(4,4,6,6,6-d5-5-Hydroxyhexyl)-3-methyl-7-(methyl-d3)-1H-purine-2,6(3H,7H)-dione (Compound 419(S)).

Separation of Enantiomers of Compound 419. Compound 419 obtained from Example 6 above (0.38 g) was dissolved in iPrOH (6 mL, HPLC grade, heating required) and diluted with hexane (4 mL, HPLC grade). Enantiomeric separation was achieved using a Waters HPLC system equipped with a preparative Daicel Chiralpak AD column (20x250 mm). For the first minute of the run, the mobile phase was 80% hexane and 20% iPrOH along with 0.1% diethylamine. After the first minute a gradient to 75% hexane and 25% iPrOH along with 0.1% diethylamine over 15 minutes was used, followed by holding at this solvent ratio for 17 minutes at a flow rate of 18 mL/min. This method resulted in baseline separation with 419(R) eluting first (21.0 min), followed by 419(S) (24.1 min). Fractions containing each enantiomer were concentrated under reduced pressure to give 0.16 g each of 419(R) (mp 107.8-108.8°C) and 419(S) (mp 108.3-108.4°C) as off-white solids.
corresponding to the presence or absence of hydrogens on the N-methyl group at the 7 position (R') of the purine ring was not possible.

Example 8

Synthesis of (±)-8-d$_1$-1-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3-methyl-7-(methyl-d$_3$)-1H-purine-2,6(3H,7H)-dione (Compound 435)

To a solution of Compound 409 (0.50 g, 1.7 mmol, 1.0 equiv) in EtOD (13 mL, Aldrich 99.5 atom % D) was added NaBD$_4$ (0.08 g, 1.9 mmol, 1.1 equiv, Cambridge Isotope Labs, 99 atom % D). A white suspension resulted, and concentrated under reduced pressure to give 0.12 g each of 435(R) and 435(S) as off-white solids.

Separation of Enantiomers of Compound 435. Compound 435 obtained from Example 8 above (0.32 g) was dissolved in a minimal amount of iPrOH (5 mL, HPLC grade, heating was required) and diluted with hexane (4 mL, HPLC grade). Enantiomer separation was achieved using a Waters HPLC system equipped with a preparative Daicel CHIRALPAK® AD column (20x250 mm). For the first minute of the run, the mobile phase was 80% hexane and 20% iPrOH along with 0.1% diethylamine. After the first minute a gradient to 75% hexane and 25% iPrOH along with 0.1% diethylamine over 15 minutes was used, followed by holding at this solvent ratio for 17 minutes at a flow rate of 18 mL/min. This method resulted in baseline separation with Compound 435(R) eluting first (21.9 min), followed by Compound 435(S) (25.2 min). Fractions containing each enantiomer were concentrated under reduced pressure to give 0.12 g each of 435(R) (mp 108.0-108.1° C.) and 435(S) (mp 107.6-107.7° C) as off-white solids.

A). (R)-8-d$_1$-1-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3-methyl-7-(methyl-d$_3$)-1H-purine-2,6(3H,7H)-dione (Compound 435(R)). $^1$H-NMR (300 MHz, CDCl$_3$): δ 1.40-1.48 (m, 3H), 1.66-1.70 (m, 2H), 3.58 (s, 3H), 4.02 (t, J 7.5, 2H), 107.67, 148.80, 151.54, 155.41. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 btm C18-RP column gradient isocratic method 78% hexane/22% isopropanol/0.01% diethylamine for 40 min at 1.00 mL/min; Wavelength: 254 nm): retention time: 3.25 min; 99.8% purity. Chiral HPLC (method: CHIRALPAK® AD 25 cm column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 254 nm): retention time: 27.24 min (major enantiomer); 31.11 min (expected for minor enantiomer): >99.9% ee purity. MS (M+H): 291.3, (M+Na): 313.2. Elemental Analysis: Calculated: C 53.78, H 6.94, N 19.30. Found: C=54.01, H=6.79, N=19.30.

B). (S)-8-d$_1$-1-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3-methyl-7-(methyl-d$_3$)-1H-purine-2,6(3H,7H)-dione (Compound 435(S)). $^1$H-NMR (300 MHz, CDCl$_3$): δ 1.41-1.48 (m, 3H), 1.62-1.72 (m, 2H), 3.58 (s, 3H), 4.03 (t, J 7.4, 2H), 107.69, 148.82, 151.58, 155.43. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 254 nm): retention time: 27.24 min (major enantiomer); 31.11 min (expected for minor enantiomer): >99.9% ee purity. MS (M+H): 291.3, (M+Na): 313.2. Elemental Analysis: Calculated: C=53.78, H=6.94, N=19.30. Found: C=54.01, H=6.79, N=19.30.
mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 254 nm); retention time: 3.25 min; 99.5% purity.

Chiral HPLC (method: CHIRALPAK® AD 25 cm column—isocratic method 78% hexane/22% isopropanol/0.01% diethylamine for 40 min at 1.00 mL/min; Wavelength: 254 nm); retention time: 31.11 min (major enantiomer); 27.24 min (expected for minor enantiomer); >99.9% ee purity. MS (M+H): 291.3, (M+Na): 313.2. Elemental Analysis (C\textsubscript{13}H\textsubscript{10}D\textsubscript{10}N\textsubscript{4}O\textsubscript{3}): Calculated: C 53.78, H 6.94, N 19.30. Found: C 54.01, H 7.11, N 18.78.

Example 10

Synthesis of 8-d1-3,7-Dimethyl-1-(4,4,6,6,6-d\textsubscript{5}-5-oxohexyl)-1\textsubscript{H}-purine-2,6(3H,7H)-dione (Compound 407)

Scheme 18. Preparation of Compounds 407, 437(R), and 437(S).

Notable in the \textsuperscript{1}H-NMR spectrum above was the absence of the following peaks: a peak at around 1.19 ppm indicating an absence of methyl hydrogens alpha to the hydroxyl group; a peak at around 3.80 ppm indicating an absence of hydrogen at the methinyl hydroxyl position; and a singlet at around 7.51 ppm indicating an absence of hydrogen at the number 8 position on the purine ring. Due to the presence of a multiplet at 1.36-1.50 ppm and a triplet at 4.01 ppm in the above \textsuperscript{1}H-NMR spectrum, determination of the presence or absence a peak at 1.51 ppm corresponding to the presence or absence of methylene hydrogens alpha to the hydroxyl group and of a singlet peak at around 3.99 ppm corresponding to the presence or absence of hydrogens on the N-methyl group at the 7 position (R\textsuperscript{1}) of the purine ring was not possible.

Example 11

Synthesis of (\textpm)-8-d1-l-(4,4,6,6,6-d\textsubscript{5}-5-Hydroxyhexyl)-3,7-dimethyl-1\textsubscript{H}-purine-2,6(3H,7H)-dione (Compound 437)

Sodium borodeuteride (1.06 g, 25.3 mmol, Cambridge Isotopes, 99 atom % D) was added to a suspension of 407 (6.5 g, 22.9 mmol) in ethanol-d\textsubscript{1} (65 mL, Aldrich, 99.5 atom % D) at 0°C. The mixture was warmed to room temperature and
stirred until a clear solution had developed (approximately 1 hour). The reaction was quenched with a saturated solution of ammonium chloride-d$_4$ (Cambridge Isotopes, 98 atom % D) in D$_2$O (8 mL, Cambridge Isotope, 99.9 atom % D), ethanol-d$_4$ was evaporated under reduced pressure and the residue was extracted with EtOAc (160 mL). The organic phase was washed with D$_2$O (20 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure to give 4.8 g (73%) of Compound 437 as a pale yellow solid.

**Example 12**

Chiral Separation of (R)-8-d$_1$-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 437(R)) and (S)-8-d$_1$-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 437(S))

Separation of Enantiomers of Compound 437. Compound 437 was obtained from Example 11 above (1.60 g) was dissolved in iPrOH (20 mL, HPLC grade, heating required). Enantiomeric separation was achieved using a Waters HPLC system equipped with a preparative CHIRALPAK® AD column (20x250 mm Daicel, 10 µm) with a preparative CHIRALPAK® AD guard column (20x50 mm Daicel, 10 µm) preceding it. For the first minute of the run, the sample was eluted with 20% iPrOH/hexanes (henceforth, with 0.1% diethylamine as co-eluent) while ramping up from a flow rate of 15 mL/min to 18.5 mL/min. Over the next 15 minutes, the sample was eluted at a flow rate of 18 mL/min with a gradient of 20% to 25% iPrOH/hexanes. For the next 19 minutes the sample was eluted at a flow rate of 18 mL/min with 25% iPrOH/hexanes. Over the next 0.5 minutes, the sample was eluted with a flow rate of 18 mL/min with a gradient of 25% to 20% iPrOH/hexanes. For the next 4.5 minutes, the sample was eluted at a flow rate of 18 mL/min with 20% iPrOH/hexanes. This elution method resulted in baseline separation of Compound 437(R) eluting first (retention time approximately 29 minutes) and Compound 437(S) eluting second (retention time approximately 340 mg of Compound 437(R) (mp 112.0-114.5 °C.) and 375 mg of Compound 437(S) (mp 111.9-112.3 °C.) as off-white solids. [Note: only 1.0 g of 437 was injected from the solution prepared above.]

**Example 13**

Alternative synthesis of (S)-8-d$_1$-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 437(S))

Notable in the 1H-NMR spectrum above was the absence of the following peaks: a peak at around 1.19 ppm indicating an absence of methyl hydrogens alpha to the hydroxyl group; a peak at around 3.80 ppm indicating an absence of hydrogen at the methinyl hydroxyl position; and a singlet peak at around 7.51 ppm indicating an absence of hydrogen at the number 8 position on the purine ring. Due to the presence of a multiplet at 1.36-1.50 ppm in the above 1H-NMR spectrum, determination of the presence or absence a peak at 1.51 ppm corresponding to the presence or absence of methylene hydrogens alpha to the hydroxyl group was not possible.

**Scheme 19. Preparation of Compound 437(S)**

1. $\text{NaBD}_4$, Water, 0°C.
2. AcOH

1. Compound 407
2. KRED 101

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(S)-8-\text{d}_{1}-1-(4,4,5,6,6,6-\text{d}_{6}-5\text{-Hydroxyhexyl})-3,7\text{-dimethyl-1H-purine-2,6(3H,7H)}\text{-dione (Compound 437(S)).} 

D-Glucono-\delta-lactone 59 (5 g, 28.09 mmoles) was added in one portion to ice-cold water (35 mL, 0-3\textdegree C) and stirred for 10 min. A freshly prepared, ice-cold solution of NaBH\textsubscript{4} (0.294 g, 7.02 mmoles, 99\% D) in 10 mL of water was added slowly over 10 min. The reaction is slightly exothermic (2\textdegree to 10\textdegree C) and the pH of the reaction is 7.42. Stirring was continued for 30 min, with the temperature maintained at 0-3\textdegree C. by cooling. Acetic acid (0.32 mL, 5.61 mmoles) was added and stirring was continued for another 30 min.

The reaction mixture was diluted with 18 mL of water and the solution was heated to 25-30\textdegree C. KH\textsubscript{2}PO\textsubscript{4} (0.85 g) was added to the mixture and the pH was adjusted to 7 with 4M KOH solution. To the resulting mixture was added (2.5 g, 8.8 mmoles) of Compound 407. A solution of NAD (15 mg), GDH (2.5 mg), CRED 101 (25 mg) in 12.5 mL of 0.1 KH\textsubscript{2}PO\textsubscript{4} buffer was added. The resulting solution was stirred at 25-30\textdegree C. The pH of the reaction mixture was maintained between 6 and 7 by adding 4M KOH solution drop-wise as needed. HPLC monitoring of the reaction indicated that the reaction was complete after 12 hours with 99.97\% conversion by HPLC analysis. Sodium chloride (12.5 g) was added and stirred for 30 min. The mixture was extracted with ethyl acetate (3x25 mL). The organic layer was separated, filtered through a celite pad and concentrated to a small volume (~5 vol). Product solids precipitated during the concentration. The slurry was heated at 40-60\textdegree C. and heptanes (20 mL) was added over 10 minutes. The slurry was stirred overnight at 20-25\textdegree C. and filtered. The wet cake dried at 50\textdegree C. for 12 hours to afford 437(R) as a white solid. (2.12 g, 85\% yield). The isolated product purity was determined to be >99.5\% by HPLC and as a single enantiomer by chiral HPLC analysis. Sodium chloride (12.5 g) was added slowly over 10 min. A freshly prepared, ice-cold solution of NaBD\textsubscript{4} (0.294 g, 7.02 mmoles, 99\% D) in 10 mL of water was added slowly over 10 min. The reaction is slightly exothermic (2\textdegree to 10\textdegree C) and the pH of the reaction is 7.42. Stirring was continued for 30 min, with the temperature maintained at 0-3\textdegree C. by cooling. Acetic acid (0.32 mL, 5.61 mmoles) was added and stirring was continued for another 30 min.

The reaction mixture was diluted with 18 mL of water and the solution was heated to 25-30\textdegree C. KH\textsubscript{2}PO\textsubscript{4} (0.85 g) was added to the mixture and the pH was adjusted to 7 with 4M KOH solution. To this was added 2.5 g (8.8 mmoles) of Compound 407. A solution of NADP (15 mg), GDH (2.5 mg), CRED A311-NADP (25 mg) in 12.5 mL of 0.1 KH\textsubscript{2}PO\textsubscript{4} buffer was added. The resulting solution was stirred at 25-30\textdegree C. The pH of the reaction mixture was maintained between 6 and 7 by adding 4M KOH solution drop-wise. The reaction was monitored by HPLC and was complete after 12 hours with 99.97\% conversion by HPLC. Sodium chloride (12.5 g) was added and stirred for 30 min. The mixture was extracted with ethyl acetate (3x25 mL). The organic layer was separated, filtered through celite pad and concentrated to a small volume (~5 vol) and product solids were precipitated. Heptanes (20 mL) were added to the slurry (at 40-60\textdegree C.) over 10 minutes. The slurry was stirred overnight at 20-25\textdegree C. and filtered. The wet cake was dried at 50\textdegree C. for 48 hours to afford 437(R) as a white solid. (2.12 g, 85\% yield). The isolated product purity was >99.95\% by HPLC and as a single enantiomer by chiral HPLC.
Example 15

Synthesis of (+)-1-(5-d1-5-Hydroxyhexyl)-3-methyl-7-(methyl-d3)-1H-purine-2,6(3H,7H)-dione (Compound 131)

Scheme 20. Preparation of Compounds 131, 131(R), and 131(S).

NaBD₄
EtOH

Example 16

Chiral Separation of (R)-1-(5-d₁-5-Hydroxyhexyl)-3-methyl-7-(methyl-d₃)-1H-purine-2,6(3H,7H)-dione (Compound 131(R)) and (S)-1-(5-d₁-5-Hydroxyhexyl)-3-methyl-7-(methyl-d₃)-1H-purine-2,6(3H, 7H)-dione (Compound 131(S))

Separation of Enantiomers of Compound 131. A portion of racemic Compound 131 obtained from Example 15 above was separated in the same manner as racemic Compound 437 above, to afford separated enantiomers Compound 131(R) (mp 112.2-112.7°C) (210 mg) and Compound 131(S) (mp 112.0-112.1°C) (220 mg).

A. (R)-1-(5-d₁-5-Hydroxyhexyl)-3-methyl-7-(methyl-d₃)-1H-purine-2,6(3H,7H)-dione (Compound 131(R)).

¹H-NMR (300 MHz, CDCl₃): δ 1.19 (s, 3H), 1.39-1.56 (m, 5H), 1.64-1.74 (m, 2H), 3.58 (s, 3H), 4.03 (t, J=7.3, 2H), 7.51 (s, 1H).
¹³C-NMR (75 MHz, CDCl₃): δ 22.87, 23.40, 27.89, 29.71, 38.64, 41.13, 107.68, 141.40, 148.76, 151.52, 155.39.
HPLC (method: Waters Atlantis T3 2.1×50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 305 nm): retention time: 3.29 min; 99.9% purity. Chiral HPLC (method: CHIRALPAK® AD 25 cm column—isocratic method 78% hexane/22% isopropanol/0.01% diethylamine for 40 min at 1.00 mL/min; Wavelength: 254 nm): retention time: 25.14 min (major enantiomer); 28.51 min (expected for minor enantiomer): >99.9% ee purity. MS (M+H): 285.3, (M+Na): 307.2. Elemental Analysis (C₁₃H₁₆D₄N₄O₃): Calculated: C 54.92, H 7.09, N 19.71. Found: C 54.67, H 7.04, N 19.32.

Notable in the ¹H-NMR spectrum above was the absence of a peak at around 3.80 ppm indicating an absence of hydrogen at the methinyl hydroxyl position. Due to the presence of a triplet at 4.01 ppm in the above ¹H-NMR spectrum, determination of the presence or absence of a singlet peak at around 3.99 ppm corresponding to the presence or absence of hydrogens on the N-methyl group at the 7 position (R¹) of the purine ring was not possible.

B. (S)-1-(5-d₁-5-Hydroxyhexyl)-3-methyl-7-(methyl-d₃)-1H-purine-2,6(3H,7H)-dione (Compound 131(S)).

¹H-NMR (300 MHz, CDCl₃): δ 1.18 (s, 3H), 1.39-1.55 (m, 5H), 1.67-1.72 (m, 2H), 3.58 (s, 3H), 4.03 (t, J=7.3, 2H), 7.51 (s, 1H).
¹³C-NMR (75 MHz, CDCl₃): δ 23.10, 23.63, 28.12, 29.94, 38.87, 41.36, 107.91, 141.63, 148.89, 151.75, 155.62. HPLC (method: Waters Atlantis T3 2.1×50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 305 nm): retention time: 3.29 min; 99.9% purity. Chiral HPLC (method: CHIRALPAK® AD 25 cm column—isocratic method 78% hexane/22% isopropanol/0.01% diethylamine for 40 min at 1.00 mL/min; Wavelength: 254 nm): retention time: 28.51 min (major enantiomer); 25.14 min (expected for minor enantiomer): >99.9% ee purity. MS (M+H): 285.3, (M+Na): 307.2. Elemental Analysis (C₁₃H₁₆D₄N₄O₃): Calculated: C 54.92, H 7.09, N 19.71. Found: C 54.65, H 7.04, N 19.32.

Notable in the ¹H-NMR spectrum above was the absence of a peak at around 3.80 ppm indicating an absence of hydrogen at the methinyl hydroxyl position. Due to the presence of a triplet at 4.01 ppm in the above ¹H-NMR spectrum, determination of the presence or absence of a singlet peak at around 3.99 ppm corresponding to the presence or absence of hydrogens on the N-methyl group at the 7 position (R¹) of the purine ring was not possible.
Synthesis of (+)-(4,4,6,6,6-ds-5-hydroxyhexyl)-3,7-dimethyl-8-d-1H-purine-2,6(3H,7H)-dione (Compound 421)

Scheme 21. Preparation of Compounds 421, 421(R), and 421(S).

obtained as described above was separated in the same manner as racemic Compound 437 (see Example 12) to afford separated enantiomers Compound 421(R) (560 mg) and Compound 421(S) (520 mg).

A. (R)-1-(4,4,6,6,6-ds-5-hydroxyhexyl)-3,7-dimethyl-8-d-1H-purine-2,6(3H,7H)-dione (Compound 421(R)).

1H-NMR (300 MHz, CDCl3): δ 1.37-1.48 (m, 2H), 1.64-1.74 (m, 3H), 3.58 (s, 3H), 3.79 (s, 1H), 3.99 (s, 3H), 4.03 (t, J = 7.4, 2H). 13C-NMR (75 MHz, CDCl3): δ 22.7, 28.1, 29.7, 33.60, 41.14, 67.6, 107.64, 148.7, 151.5, 155.38. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN40% formic acid in 14 minutes (1.0 mL/min) with 4 minute hold at 95% ACN; Wavelength: 254 nm): retention time: 3.33 min; >99.9% purity. Chiral HPLC (method: CHIRALPAK® AD 25 cm column—isocratic method 78% hexane/22% isopropanol/0.1% diethylamine for 40 minutes at 1.00 mL/min; Wavelength: 254 nm): retention time: 28.16 min (expected for S enantiomer): >99.9% ee purity. MS (M+H-H2O): 269.1; (M+H): 287.1; (M+Na): 309.3.

B. (S)-1-(4,4,6,6,6-ds-5-hydroxyhexyl)-3,7-dimethyl-8-d-1H-purine-2,6(3H,7H)-dione (Compound 421(S)).

1H-NMR (300 MHz, CDCl3): δ 1.37-1.48 (m, 2H), 1.64-1.74 (m, 3H), 3.58 (s, 3H), 3.79 (s, 1H), 3.99 (s, 3H), 4.03 (t, J = 7.4, 2H). 13C-NMR (75 MHz, CDCl3): δ 22.7, 28.1, 29.7, 33.60, 41.14, 67.6, 107.64, 148.7, 151.5, 155.38. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN40% formic acid in 14 minutes (1.0 mL/min) with 4 minute hold at 95% ACN; Wavelength: 254 nm): retention time: 3.34 min; >99.9% purity. Chiral HPLC (method: CHIRALPAK® AD 25 cm column—isocratic method 78% hexane/22% isopropanol/0.1% diethylamine for 40 minutes at 1.00 mL/min; Wavelength: 254 nm): retention time: 28.16 min (S enantiomer): >99.9% ee purity. MS (M+H-H2O): 269.1; (M+H): 287.1; (M+Na): 309.3.


Notable in the 1H-NMR spectrum of both 421(R) and 421(S) was the absence of a peak at around 7.51 ppm, indicating an absence of hydrogen at the 2-position on the imidazole ring system.

Alternative Preparation of 421(R):

Synthesis of (+)-(4,4,6,6,6-ds-5-hydroxyhexyl)-3,7-dimethyl-8-d-1H-purine-2,6(3H,7H)-dione (Compound 421).

Following the same general method as for the synthesis of Compound 437 in Example 11 above, Compound 407 (see Example 10) was treated with NaBH4 in EtOD and extracted with CH2Cl2 to afford Compound 421.

Example 18

Chiral Separation of (R)-1-(4,4,6,6,6-ds-5-hydroxyhexyl)-3,7-dimethyl-8-d-1H-purine-2,6(3H,7H)-dione (Compound 421(R)) and (S)-1-(4,4,6,6,6-ds-5-hydroxyhexyl)-3,7-dimethyl-8-d-1H-purine-2,6(3H,7H)-dione (Compound 421(S))

Separation of Enantiomers 421(R) and 421(S) from (+) Compound 421. A portion of racemic Compound 421
Preparation of Compound 421 (R) from Compound 407 Using CRED A131

A 100 mL 3-necked RB flask equipped with a heating mantle, a J-Kem thermocouple, magnetic stir bar, a reflux condenser, and a pH probe was charged with 407 (500 mg, 1.75 mmol), D(+) Glucose (750 mg, 1.5 wt) in 10 mL buffer (0.1M KH$_2$PO$_4$, pH=7.0) and heated to 25-30°C. A solution of NADP (15 mg, 3 wt %), GDH (3 mg, 0.6 wt %), ALMAC CRED A311-NADP (30 mg, 6 wt %) in 0.1 M KH$_2$PO$_4$ buffer was added and maintained reaction temperature 25-30°C. To this added 1 mL of methyl-t-butyl ether (MTBE). The pH of the reaction mixture was maintained between 6 and 7 adding 4M KOH solution drop-wise. The reaction was monitored by HPLC and was complete after 29 hours with 99.87% conversion by HPLC. Sodium chloride (2.5 g, 5 wt) was added and stirred for 20 min. The reaction mixture was extracted with ethyl acetate (3 x 15 mL). The organic layer was separated, filtered through celite pad and concentrated to a small volume (~5 vol) and product solids were precipitated. Heptanes (5 mL) was added to the slurry (at 40-60°C) over 5 minutes. The slurry was stirred at 20-25°C. The wet cake was dried at 50°C for 12 hours to afford 421(R) as a white solid. (0.422 g, 84% yield). The isolated product purity was >99.5% by HPLC and single enantiomer by chiral HPLC.

Example 19

Synthesis of (±)-1-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 137)

Scheme 22. Preparation of Compound 137.

Synthesis of (±)-1-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 137).

Example 20

Synthesis of (R)-1-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 137(R))

Scheme 23. Preparation of Compound 137(R).

Synthesis of (R)-1-(4,4,5,6,6,6-d$_6$-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 137(R)).
A solution of 437(R) (650 mg, 2.26 mmol, see Example 12) and K₂CO₃ (320 mg, 2.3 mmol) in water (40 mL) was heated at 110°C (bath temperature) for 26 hours. The solution was concentrated to dryness, redissolved in water (30 mL) and heated to 100°C for a further 6 hours. After cooling to ambient temperature the solution was extracted with CH₂Cl₂ (4x50 mL). The organic solution was dried (Na₂SO₄), filtered, concentrated, then dried under vacuum to afford 565 mg of 137(R) as an off-white solid.

Compound 137(R) in Example 20 above, a portion of Compound 137(S) was converted to 310 mg of 137(R) as an off-white solid.

A solution of 437(R) (650 mg, 2.26 mmol, see Example 12) and K₂CO₃ (320 mg, 2.3 mmol) in water (40 mL) was heated at 110°C (bath temperature) for 26 hours. The solution was concentrated to dryness, redissolved in water (30 mL) and heated to 100°C for a further 6 hours. After cooling to ambient temperature the solution was extracted with CH₂Cl₂ (4x50 mL). The organic solution was dried (Na₂SO₄), filtered, concentrated, then dried under vacuum to afford 565 mg of 137(R) as an off-white solid.

Compound 137(R) in Example 20 above, a portion of Compound 137(S) was isolated. HPLC purity was 99.92%.
Example 24

S-1-(4,4,6,6,6-ds-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 121(S))

Following the same general method as for the synthesis of Compound 137(R) in Example 20 above, a portion of Compound 421(S) (see Example 18) was converted to 590 mg of Compound 121(S).

Alternatively, Compound 121(S) is synthesized from pentoxifylline (58) in a two step method according to Scheme 22a:

Step 1. Pentoxifylline (58; 1 mol equiv) was combined with toluene (20 volumes).
added D$_2$O (1.5 volumes) and potassium carbonate (0.25 equiv) and the mixture was heated to reflux (ca. 87°C) for 3-4 hrs. The mixture was cooled to 40-50°C and the aqueous layer was removed. To the remaining toluene solution was added D$_2$O (1.5 volumes) and potassium carbonate (0.25 equiv) and the mixture was heated to reflux (ca. 87°C) for 3-4 hrs. The mixture was cooled to 40-50°C and the aqueous layer was removed. To the remaining toluene solution was added D$_2$O (1.5 volumes) and potassium carbonate (0.25 equiv) and the mixture was heated to reflux (ca. 87°C) for 3-4 hrs. The mixture was cooled to 40-50°C and the aqueous layer was removed. The organic layer was concentrated to ca. 5 volumes below 45°C, was cooled to 20-25°C and then heptane (1 volume) was added, followed by stirring at 20-25°C for 30 min. The slurry was filtered and washed with heptane, followed by drying in vacuo at 40-50°C to a constant weight. The yield of Compound 407 was approximately 90%.

Step 2. Compound 421(S). A 3-necked 12-L RB flask equipped with a heating mantle, a J-Kem thermocouple, a mechanical stirrer, and a pH probe was charged with glucose (547.5 g, Aldrich lot #088K0039) followed by 3.47 L of 0.1M KH$_2$PO$_4$, pH=7.0 (“Buffer”; 9.5 vol). The reaction mixture was stirred to dissolve all solids. A mixture of Compound 407 (365 g) in Buffer (2.92 L) was added and the container was rinsed with Buffer (1.28 L). The rinse was added to the reactor. Initially, the reaction mixture was a very thin milky suspension. A solution of KRED-NADH-101 (3.65 g, CODEXIS lot #1021908WW), NAD (2.19 g, SPECTRUM KH2PO4, pH=7.0, same as below). The reaction mixture was stirred to dissolve all solids. A solution of glucose (558 g, Aldrich lot #088K0039) in buffer (2 L) was added in one portion followed by a solution of NAD (19.25 g, Spectrum lot #YA0655) in buffer (500 mL), and a solution of GDH (1.5 g, ALMAC lot #IM-1311-131-1) in buffer (500 mL). The initial reaction mixture was pH 6.98. A mixture of Compound 407 in buffer (3 L) at 30°C was added to the reaction mixture and the container was rinsed with Buffer (1.6 L). The rinse was charged to the reactor. The pH of the reaction mixture was 6.99. The reaction mixture was warmed to 30°C and monitored by pH meter. The reaction temperature was kept at 29.0 to 31.5°C and the pH of the reaction mixture was kept between pH 6.93 and pH 7.02 by adding 4M KOH solution drop-wise as needed. The reaction was complete after 22 hours with 99.96% conversion as determined by HPLC. The chiral HPLC analysis of the resulting product showed the chiral selectivity was 99.85% to the desired S-alcohol.

[2] The reaction mixture was mixed with NaCl (2 kg) and extracted with EtOAc (1×4 L and 3×2 L). During the first extraction, a rag layer was formed and the reaction mixture was filtered through a cellite pad. No further issues with phase separation were encountered after the filtration. The combined organic extracts were concentrated to about 1.5 L at 50-60°C and n-heptane (2 L) was added to precipitate the solids. The slurry was cooled to 20°C and filtered. The flask was rinsed with filtrate to complete the transfer. The filter cake was washed with n-heptane (2x500 mL) and dried over the weekend at 40-50°C to afford Compound 421(S) (366 g, 94% yield). The product was analyzed by HPLC (99.95% purity), chiral HPLC (99.88/0.12 S/R), and 1H NMR (99.5% “D” incorporation at the methyl position).

Step 3. Compound 121(S). In a 3-L 3-necked RB flask, Compound 421(S) (100 g) was charged followed by water (1.0 L) and KH$_2$PO$_4$ (0.25 equiv). The reaction mixture was heated to 80±5°C and monitored by 1H NMR. The reaction was complete after 24 hours and worked up after 65 hours. The resulting product was extracted with three times with EtOAc and the solid products from the three extractions combined and re-dissolved in 5 volumes of EtOAc at 60-65°C. n-heptane (5.5 vol.) was added at 60-65°C over 15 minutes and cooled to 20°C over night (16 hrs). The slurry was filtered and the wet cake was washed with n-heptane (2x1 L vol.) and afforded only 4.8 g of Compound 421(S) (1.3% yield) of product as a white solid. The combined mother liquor was concentrated to afford 2.0 g of Compound 421(S) as a yellow solid (0.5% yield). The isolated product was a very high quality (100% purity by HPLC) and a single enantiomer (100/0 S/R % by chiral HPLC) from the main lot with 99.5% “D” incorporation at the methyl position by 1H NMR.
Example 25

**Synthesis of 3,7-Dimethyl-1-(4,4,6,6,6-d₆-5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (Compound 107)**


![Scheme 25](image)

**Example 26**

**Synthesis of (_+)-1-(4,4,5,6,6,6-d₆-5-Hydroxyhexyl)-3,7-di(methyl-d₃)-1H-purine-2,6(3H,7H)-dione (Compound 434)**

![Scheme 26](image)

**Example 27**

**Chiral Separation of (R)-1-(4,4,5,6,6,6-d₆-5-Hydroxyhexyl)-3,7-di(methyl-d₃)-1H-purine-2,6(3H,7H)-dione (Compound 434(R)) and (S)-1-(4,4,5,6,6,6-d₆-5-Hydroxyhexyl)-3,7-di(methyl-d₃)-1H-purine-2,6(3H,7H)-dione (Compound 434(S))**

![Separation of Enantiomers](image)
Synthesis of (±)-1-(4,4,5,6,6,6-d6-5-hydroxyhexyl)-3-methyl-7-methyl-d3-1H-purine-2,6(3H,7H)-dione (Compound 135). Following the same general method as for the synthesis of Compound 137 in Example 19 above, a portion of Compound 435 (see Example 8) was converted to 0.99 g of Compound 135.

Example 29

Chiral Separation of (R)-1-(4,4,5,6,6,6-d6-5-hydroxyhexyl)-3-methyl-7-methyl-d3-1H-purine-2,6(3H,7H)-dione (Compound 135(R)) and (S)-1-(4,4,5,6,6,6-d6-5-hydroxyhexyl)-3-methyl-7-methyl-d3-1H-purine-2,6(3H,7H)-dione (Compound 135(S))

Separation of Enantiomers of Compound 135. A portion of racemic Compound 135 obtained as described above was separated in the same manner as racemic Compound 437 (see Example 12) to afford separated enantiomers Compound 135(R) (352 mg) and Compound 135(S) (343 mg).

A. (R)-1-(4,4,5,6,6,6-d6-5-hydroxyhexyl)-3-methyl-7-methyl-d3-1H-purine-2,6(3H,7H)-dione (Compound 135(R)). 1H-NMR (300 MHz, CDCl3): δ 1.41-1.48 (m, 2H), 1.64-1.74 (m, 3H), 3.58 (s, 3H), 4.02 (t, J=7.4, 2H), 7.50 (s, 1H). 13C-NMR (75 MHz, CDCl3): δ 22.65, 27.84, 29.68, 41.12, 107.67, 141.38, 148.76, 151.52, 155.37. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 minutes (1.0 mL/min) with 4 minute hold at 95% ACN; Wavelength: 305 nm): retention time: 25.21 min (R enantiomer); 28.42 min (expected for S enantiomer); >99.5% ee purity. MS (M+H): 272.1; (M+H2O): 290.1; (M+Na): 312.3. Elemental Analysis (C13H11D9N4O3): Calculated: C 53.97, H 6.97, N 19.36. Found: C 53.93, H 7.03, N 19.29.

B. (S)-1-(4,4,5,6,6,6-d6-5-hydroxyhexyl)-3-methyl-7-methyl-d3-1H-purine-2,6(3H,7H)-dione (Compound 135(S)). 1H-NMR (300 MHz, CDCl3): δ 1.38-1.48 (m, 2H), 1.64-1.74 (m, 3H), 3.58 (s, 3H), 4.02 (t, J=7.4, 2H), 7.50 (s, 1H). 13C-NMR (75 MHz, CDCl3): δ 22.65, 27.84, 29.68, 41.12, 107.67, 141.38, 148.76, 151.52, 155.37. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 minutes (1.0 mL/min) with 4 minute hold at 95% ACN; Wavelength: 305 nm): retention time: 25.27 min; 99.8% purity. Chiral HPLC (method: CHIRALPAK® AD 25 cm column—isocratic method 78% hexane/22% isopropanol/0.1% diethylamine for 40 minutes at 1.00 mL/min; Wavelength: 254 nm): retention time: 25.27 min (R enantiomer); 28.42 min (expected for S enantiomer); >99.9% ee purity. MS (M+H): 272.1; (M+H2O): 290.1; (M+Na): 312.3. Elemental Analysis (C13H11D9N4O3): Calculated: C=53.97, H=6.97, N=19.36. Found: C=53.83, H=6.98, N=19.30. 
Example 30

Synthesis of (±)-1-(5-Hydroxyhexyl)-3-methyl-7-methyl-d3-1H-purine-2,6(3H,7H)-dione (Compound 116)

Following the same general method as for the synthesis of Compound 437 in Example 11 above, Compound 100 (see Example 1) was treated with NaBH4 in EtOH and extracted with CH2Cl2 to afford Compound 116.

MS (M+H2O): 266.1; (M+H): 284.1; (M+Na): 306.0.

Example 31

Synthesis of (±)-1-(5-d1-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 133) and of the (R) and (S) enantiomers of Compound 133

Scheme 28. Preparation of Compounds 133, 133(S) and 133(R).

Separation of Enantiomers of Compound 133. A portion of racemic Compound 133 obtained from Example 31 above was separated in the same manner as racemic Compound 437 (see Example 12), to afford separated enantiomers. Compound 133(R) (mp 112.9-113.1°C) (290 mg) and Compound 133(S) (mp 112.1-112.2°C) (302 mg).

A. (R)-1-(5-d1-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 133(R)). 1H-NMR (300 MHz, CDCl3): δ 1.18 (s, 3H), 1.40-1.54 (m, 3H), 1.65-1.72 (m, 2H), 3.58 (s, 3H), 3.99 (s, 3H), 4.03 (t, J=7.5, 2H), 7.50 (s, 1H). 13C-NMR (75 MHz, CDCl3): δ 23.47, 24.00, 28.50, 30.30, 34.19, 39.25, 41.73. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 305 nm): retention time: 3.31 min; >99% purity. MS (M+H): 282.0. Elemental Analysis (C13H19DN4O3): Calculated: C=55.50, H=7.17, N=19.92. Found: C=55.4, H=7.34, N=19.72.

B. (S)-1-(5-d1-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 133(S)). 1H-NMR (300 MHz, CDCl3): δ 1.18 (s, 3H), 1.40-1.54 (m, 3H), 1.65-1.72 (m, 2H), 3.59 (s, 3H), 3.99 (s, 3H), 4.03 (t, J=7.5, 2H), 7.50 (s, 1H). 13C-NMR (75 MHz, CDCl3): δ 23.47, 24.00, 28.50, 30.30, 34.19, 39.25, 41.73, 142.01. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 305 nm): retention time: 3.31 min; >99% purity. MS (M+H): 282.0. Elemental Analysis (C13H19DN4O3): Calculated: C=55.50, H=7.17, N=19.92. Found: C=55.3, H=7.02, N=19.83.

Notable in the 1H-NMR spectrum above was the absence of a peak at around 3.80 ppm indicating an absence of hydrogen at the methinyl hydroxyl position.

Example 32

Chiral Separation of (R)-1-(5-d1-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 133(R)) and (S)-1-(5-d1-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 133(S))

Separation of racemic Compound 133 obtained from Example 31 above was performed in the same manner as racemic Compound 437 (see Example 12), to afford purified enantiomers. Compound 133(R) (mp 112.9-113.1°C) (290 mg) and Compound 133(S) (mp 112.1-112.2°C) (302 mg).

A. (R)-1-(5-d1-5-Hydroxyhexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione (Compound 133(R)). 1H-NMR (300 MHz, CDCl3): δ 1.18 (s, 3H), 1.40-1.54 (m, 3H), 1.65-1.72 (m, 2H), 3.58 (s, 3H), 3.99 (s, 3H), 4.03 (t, J=7.5, 2H), 7.50 (s, 1H). 13C-NMR (75 MHz, CDCl3): δ 23.47, 24.00, 28.50, 30.30, 34.19, 39.25, 41.73. HPLC (method: Waters Atlantis T3 2.1x50 mm 3 μm C18-RP column—gradient method 5-95% ACN+0.1% formic acid in 14 min (1.0 mL/min) with 4 min hold at 95% ACN+0.1% formic acid; Wavelength: 305 nm): retention time: 3.31 min; >99% purity. MS (M+H): 282.0. Elemental Analysis (C13H19DN4O3): Calculated: C=55.50, H=7.17, N=19.92. Found: C=55.3, H=7.02, N=19.83.

Notable in the 1H-NMR spectrum above was the absence of a peak at around 3.80 ppm indicating an absence of hydrogen at the methinyl hydroxyl position.
Example 33

Synthesis of 3,7-dimethyl-1-(6,6,6-d3-5-hydroxyhexyl)-1H-purine-2,6(3H,7H)-dione (Compound 157) and (S)-3,7-dimethyl-1-(6,6,6-d3-5-hydroxyhexyl)-1H-purine-2,6(3H,7H)-dione (Compound 156(S)).

Scheme 29: Preparation of Compounds 157 and 156(S).

Step 1. 5-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-N-methoxy-N-methylpentanamide (61). To a 100 mL round-bottom flask equipped with a magnetic stirrer and thermocouple was added 50 (1.49 g, 8.27 mmol, 1.0 eq) and DMSO (40 mL). The mixture was stirred at room temperature for 30 mins. EtOAc (10 mL) was added and the mixture was filtered through a medium-porosity funnel, an MTBE rinse (2x10 mL), and then a solid residue was precipitated, but less solid was present than prior to heating. Solid NaCl (~3 g) was added and the mixture stirred for another 30 mins. The mixture was filtered through a medium-porosity funnel, an MTBE rinse (2x10 mL), and then a solid residue was obtained after removing the organic volatile in a rotovap. The solid residue was suspended in MTBE (25 mL), the mixture was stirred at room temperature for 1 hr, then at room temperature for another hour, followed by filtration via a medium-porosity funnel, an MTBE rinse (2x10 mL), and drying under vacuum. The product was collected as a white solid with an AUC purity of 99.2 A%.

Step 2. 3,7-dimethyl-1-(6,6,6-d3-5-hydroxyhexyl)-1H-purine-2,6(3H,7H)-dione (Compound 157). To a 100 mL, 3-neck round-bottom flask equipped with a magnetic stirrer and thermocouple was added 61 (1.30 g, 4.01 mmol, 1.0 eq) and THF (45 mL). The mixture was stirred and heated to about 150°C. To dissolve all materials, then was cooled to 0°C. (note: a solid precipitated, but less solid was present than prior to heating). CD3Mgl was added (1.0 M in Et2O, 8.82 mL, 2.2 eq) via syringe, at such a rate that the internal temperature did not rise above 5°C. After the addition was complete, the mixture was stirred at 0°C for 30 mins, then the cold bath was removed and the mixture was allowed to warm up to room temperature.

The mixture was stirred at room temperature for 1.5 hrs, whereupon IPC analysis by HPLC indicated conversion was 80 A%. Further stirring at room temperature for 1.5 hrs afforded no additional conversion, as shown by another IPC analysis. The mixture was cooled to 0°C, and CD3Mgl (1.0 M in Et2O, 2.0 mL, 0.5 eq) was added via a syringe. The mixture was warmed to room temperature overnight. The next day, IPC analysis by HPLC indicated that conversion was greater than 95 A%. The reaction mixture was quenched with 0.5 N aqueous citric acid (40 mL) and extracted with MTBE (60 mL). The phases were separated and the organic layer was washed with water (20 mL), aq. satd. NaHCO3 (20 mL), then water (20 mL). The organic layer was concentrated in a rotovap to afford crude product with an AUC purity at 91 A%. Further purification was carried out by slurrying in MTBE (5 mL) at room temperature overnight. The desired product was obtained as 0.92 g (81%) of a white solid with an AUC purity of >95 A%. 1H-NMR: δ 1.61-1.71 (m, 4H), 2.50 (t, J=7.1, 2H), 3.57 (s, 3H), 3.98 (s, 3H), 4.01 (t, J=7.1, 2H), 7.50 (s, 1H).

Notable in the 1H-NMR spectrum above was the absence of a singlet at around 2.15 ppm, indicating an absence of methyl ketone hydrogens.

Step 3. (S)-3,7-dimethyl-1-(6,6,6-d3-5-hydroxyhexyl)-1H-purine-2,6(3H,7H)-dione (Compound 156). To a 100 mL, 3-neck round-bottom flask equipped with a magnetic stirrer and thermocouple was added Compound 157 (563 mg, 2.00 mmol, 1.0 eq), D (+)-glucose (844 mg), and 0.1 M KH2PO4. The mixture was stirred at room temperature, pH = 6-7. Further purification was carried out by slurrying in MTBE (5 mL) at room temperature overnight. The desired product was obtained as 0.55 g (82%) of an uncolored solid with an AUC purity of >95 A%. 1H-NMR: δ 1.61-1.71 (m, 4H), 2.50 (t, J=7.1, 2H), 3.57 (s, 3H), 3.98 (s, 3H), 4.01 (t, J=7.1, 2H), 7.50 (s, 1H).

Notable in the 1H-NMR spectrum above was the absence of a singlet at around 2.15 ppm, indicating an absence of methyl ketone hydrogens.

Step 4. (S)-3,7-dimethyl-1-(6,6,6-d3-5-hydroxyhexyl)-1H-purine-2,6(3H,7H)-dione (Compound 156). To a 100 mL, 3-neck round-bottom flask equipped with a magnetic stirrer and thermocouple was added Compound 157 (563 mg, 2.00 mmol, 1.0 eq), D (+)-glucose (844 mg), and 0.1 M KH2PO4. The mixture was stirred at room temperature, pH = 6-7. Further purification was carried out by slurrying in MTBE (5 mL) at room temperature overnight. The desired product was obtained as 0.55 g (82%) of an uncolored solid with an AUC purity of >95 A%. 1H-NMR: δ 1.61-1.71 (m, 4H), 2.50 (t, J=7.1, 2H), 3.57 (s, 3H), 3.98 (s, 3H), 4.01 (t, J=7.1, 2H), 7.50 (s, 1H).

Notable in the 1H-NMR spectrum above was the absence of a singlet at around 2.15 ppm, indicating an absence of methyl ketone hydrogens.
a pad of wet Celite to remove a gel-like substance, and the wet filter cake was rinsed with EtOAc (2x10 mL). The filtrate was collected and the phases were separated. The aqueous layer was washed with EtOAc (2x60 mL). The combined organic layers were concentrated to dryness in a rotovap. 527 mg of crude product were collected, affording a mass balance of 93%. The residue was purified by flash chromatography (silica gel, eluent MeOH/CH₂Cl₂, gradient 2-20% MeOH) to afford 398 mg (70%) of the desired product as a white solid with an AUC purity of 99.9%.

**1H NMR:** δ 1.45-1.57 (m, 4H), 1.63-1.74 (m, 2H), 3.57 (s, 3H), 3.76-3.83 (m, 1H), 3.98 (s, 3H), 4.02 (t, J 7.3, 2H), 7.50 (s, 1H).

Notable in the 1H-NMR spectrum above was the absence of a peak at around 1.19 ppm, indicating an absence of methyl hydrogens alpha to the hydroxyl group. Chiral HPLC analysis (method: CHIRALPAK® AD-H 25 cm column isocratic method 75% n-heptane/25% isopropanol for 25 min at 1.25 mL/min; wavelength: 274 nm): retention time: 17.5 min (major enantiomer); 15.5 min (expected for minor enantiomer); >99.95% ee purity.

**Biological Evaluation**

**Example 34a**

**Evaluation of Pharmacokinetics in Dogs Following Oral Administration. Comparison of Compound 409 and Pentoxifylline**

Metabolism of the title compounds were studied following oral administration to male beagle dogs. Blood samples were removed from dosed dogs at various time points and plasma isolated therefrom. The plasma samples were used for the determination of plasma drug levels by LC-MS/MS (liquid chromatography with tandem mass spectrometry) for estimating pharmacokinetic parameters.

Compound 409 and pentoxifylline were dissolved separately in saline to a concentration of 4 mg/mL. A 1:1 (v/v) mixture of the two solutions was prepared to yield a solution having a final concentration of 2 mg/mL of both Compound 409 and pentoxifylline.

Two male beagle dogs were fasted overnight and then orally dosed via gavage with 2.5 mg/kg of Compound 409 and pentoxifylline using the mixture described above. Blood samples (approximately 1 mL) were collected via the femoral vein at 0 min (pre-dose), 5 min, 15 min, 30 min, 45 min, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr, 8 hr, 10 hr, 12 hr, 16 hr, and 24 hr post-dose. Blood was stored on ice prior to centrifugation to obtain plasma samples. Centrifugation took place within 15 minutes of blood collection to harvest plasma (maximum volume). The plasma was decanted immediately and frozen/stored at -20°C until analysis.

**TABLE 8**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ave. Cmax (ng/mL)</th>
<th>Ave. AUC (hr*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>784</td>
<td>448</td>
</tr>
<tr>
<td>Compound 409</td>
<td>1230</td>
<td>811</td>
</tr>
<tr>
<td>% Difference</td>
<td>+57%</td>
<td>+80%</td>
</tr>
</tbody>
</table>

% Difference = |[(deuterated species) – (nondeuterated species)] / (nondeuterated species) |

Table 8 shows the results of the evaluation described in Example 34a. The average Cmax and average AUC for Compound 409, a deuterated version of pentoxifylline, were significantly greater than for pentoxifylline. The deuterated compound exhibited greater exposure in the dog plasma than pentoxifylline.

**Example 34b**

Repeat Evaluation of Pharmacokinetics in Dogs Following Oral Administration. Comparison of Compound 409 and Pentoxifylline with Monitoring of Metabolites

Example 34a was repeated with additional monitoring of the pentoxifylline and Compound 409 metabolites. In this experiment Compound 409 and pentoxifylline were dissolved separately in saline to a concentration of 4.4 and 4 mg/mL respectively. A 1:1 (v/v) mixture of the two solutions was prepared to yield a solution having a final concentration of 2.2 mg/mL of Compound 409 and 2 mg/mL pentoxifylline.

Post-dosing data analysis included adjustments to account for the 10% difference in dosing concentration between compound 409 and pentoxifylline.

Four beagle dogs (2-3 years of age, and weighed 5 to 8 kg) were fasted overnight and then orally dosed via gavage with 2.75 mg/kg Compound 409 and 2.5 mg/kg pentoxifylline using the mixture described above. Blood samples (approximately 1 mL) were collected via the femoral vein at 0 min (pre-dose), 5 min, 15 min, 30 min, 45 min, 1 hr, 1.5 hr, 2 hr, 3 hr, 4 hr, 6 hr post-dose. Blood was stored on ice prior to centrifugation to obtain plasma samples. Centrifugation took place within 15 minutes of blood collection to harvest plasma (maximum volume). The plasma was decanted immediately and frozen/stored at -20°C until analysis.

Plasma samples were analyzed by LC-MS/MS for the presence of the administered compound and its corresponding M1 metabolite.
The results from each of the four dogs are shown in FIGS. 1A and 1B. The results from one of the four dogs (Dog H, FIG. 1B) were inconsistent with that of the other three. That dog showed a 10-fold higher plasma concentration of each of the administered compounds and their respective metabolites at 5 minutes post-administration. In addition, that dog did not show a characteristic increase in plasma concentration of the administered compounds between 5 and 15 minutes post-administration. It was concluded that this dog was most likely improperly gavaged and that the compounds were probably administered through the trachea, rather than into the GI tract as would have been desired. Accordingly, the data from this dog was excluded from the analyses. The summary analysis of the three remaining dogs is shown in Table 9.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Ave. Cmax (ng/mL)</th>
<th>Ave. AUC (hr*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentoxifylline</td>
<td>166</td>
<td>69</td>
</tr>
<tr>
<td>Compound 409*</td>
<td>299</td>
<td>136</td>
</tr>
<tr>
<td>% Difference*</td>
<td>+80%</td>
<td>+97%</td>
</tr>
</tbody>
</table>

*The dosing concentration of compound 409 was 10% higher than that for pentoxifylline and hence the numbers reported here reflect the adjustment for that 10% increase.

As can be seen in Table 9, higher levels of Compound 409 in terms of Cmax and AUC were observed when compared to pentoxifylline co-dosed at the same level. FIG. 1 demonstrates that Compound 409 was more slowly cleared from the plasma than pentoxifylline in the three dogs that were orally dosed. FIGS. 1a and 1b demonstrate that Compound 409 was more slowly cleared from the plasma than pentoxifylline in the three dogs that were orally dosed. FIGS. 1a and 1b also show that overall systemic exposure to Compound 410 (the deuterated M1 metabolite of 409) following dosing of Compound 409 was greater than that of the M1 metabolite following dosing of pentoxifylline.

Example 34e

Evaluation of Pharmacokinetics in Dogs Following Oral Administration. Comparison of Compound 413 and Pentoxifylline

This study was similar to those described in Examples 34a and 34b, except that Compound 413 was evaluated. Four male beagle dogs were orally dosed by gavage with a mixture containing 2 mg/mL of each of pentoxifylline and Compound 413 in saline. Blood samples were taken as in Example 34b.

Example 41c

Evaluation of the Stability of Compounds in Rat Whole Blood. Comparison of Compounds 409, 435(S), 435(R) and Pentoxifylline and its M-1 Metabolites

This study was performed to evaluate the stability of the title compounds in rat whole blood. Because the ketone (or keto-compound; either pentoxifylline or 409) and its corresponding M-1 alcohol metabolite interconvert, levels of these components were measured after either the keto-compound was added to the blood or the M-1 was added. In other words, in some tests the keto-compound was the starting test compound and in other tests an M-1 metabolite was the starting test compound.

Fresh rat whole blood was obtained from ViviSource Laboratories, Waltham, Mass. Stock solutions (7.5 millimolar (mM)) of test compounds were prepared in dimethyl sulfoxide (DMSO). The 7.5 mM stock solutions were diluted to 500 micromolar (µM) in acetonitrile (ACN). To 990 microliters (µL) of blood pre-warmed to 37° C. for 7 minutes was added 10 µL of 500 µM test compound to a final concentration of 5 µM. The test compounds were pentoxifylline, (S)-M1 metabolite of pentoxifylline, (R)-M1 metabolite of pentoxifylline, Compound 409, Compound 435(S), and Compound 435(R). The latter two test compounds are deuterated (S)-M1 and (R)-M1 metabolites, respectively, of Compound 409. The reaction mixture was incubated at 37° C. Aliquots (50 µL) were removed at 0 min, 5 min, 15 min, 30 min, 1 hour and 2 hours following the addition of test compound and added to 96-well plates containing 150 µL of ice cold acetonitrile with an internal standard to stop the reaction. The plates were stored at −20° C. for 20 minutes after which 100 µL of 50% acetonitrile/water was added to the wells of the plate prior to centrifugation to pellet precipitated proteins. A 200-µL aliquot of each supernatant was transferred to another 96-well plate and analyzed by LC-MS/MS using an Applied Biosystems API 4000 mass spectrometer for amounts of the administered compound and its specific metabolite listed in Table 11 below.
were purchased from Sigma-Aldrich. Xenotech, LLC (Lenexa, Kans.). 

3-nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride (MgCl₂), and dimethyl sulfoxide (DMSO) were prepared in DMSO. The 7.5-nM stock solutions were diluted to 250 μM in acetonitrile (ACN). The human liver microsomes were diluted to 2.5 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM MgCl₂. The diluted microsomes were added to wells of a 96-well deep-well polypropylene plate in triplicate. 10 μL of the 250 μM test compound was added to the microsomes and the mixture was pre-warmed to 37° C. for 10 minutes. Reactions were initiated by addition of pre-warmed NADPH solution. The final reaction volume was 0.5 mL and contained 2.0 mg/mL human liver microsomes, 5 μM test compound, and 2 mM NADPH in 0.1M potassium phosphate buffer, pH 7.4, and 3 mM MgCl₂. The reaction mixtures were incubated at 37° C., and 50-μL aliquots were removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contained 50 μL of ice-cold acetonitrile with internal standard to stop the reactions. The plates were stored at 4° C. for 20 minutes after which 100 μL of water was added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants were transferred to another 96-well plate and analyzed for the amount of the administered compound and its specific metabolite (listed in Table 11 above) by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer.

The results of this study are depicted in FIGS. 2 and 3. The time course of metabolite formation is shown in FIG. 2. The relative amount of metabolite formed, as shown in FIG. 3, was calculated based on the amount present at 2 hr relative to the earliest time point at which it was detected in the incubation mixture, 5 minutes for A and B, and 15 minutes for C.

As seen in FIG. 3, after approximately 2 hours the amount of (S)-M1 formed in rat whole blood incubated with pentoxifylline (FIG. 3, column A) was similar to the amount of Compound 419(S) formed in rat whole blood incubated with Compound 409 (FIG. 3, column B). Thus, the deuterium substitution in Compound 409 had no discernable effect on the relative level of deuterated (S)-M1 metabolite (Compound 419(S)) formed as compared to the relative level of undeuterated (S)-M1 formed from undeuterated pentoxifylline.

For the reverse reaction, (S)-M1 to the keto-compound, deuterium effect on the metabolism of (R)-M1 (Compound 435(R)) reduced by almost 5-fold the amount of deuterated pentoxifylline formed (Compound 409) after 30 minute incubation with human liver microsomes as compared to the amount of undeuterated pentoxifylline formed from undeuterated (R)-M1 (comparing columns E and F in FIG. 5). FIG. 4 shows the time course of

Table 11: Compound-Metabolite Pairs Analyzed in Rat Whole Blood (Examples 35 and 36)

<table>
<thead>
<tr>
<th>Experiment Pair</th>
<th>Compound Incubated with Blood</th>
<th>Metabolite Analyzed</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>pentoxifylline</td>
<td>(S)-M1*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Compound 409</td>
<td>Compound 419(S)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>(S)-M1</td>
<td>Pentoxifylline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Compound 435(S)</td>
<td>Compound 409</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>(R)-M1</td>
<td>pentoxifylline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Compound 435(R)</td>
<td>Compound 409</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mass observed via LC-MS/MS. Stereochecmistry presumed to be ≥95% (S) based on published pentoxifylline metabolism reports.
the specific metabolite produced during incubation of the administered compound with human liver microsomes.

Example 37

Pharmacokinetic Study in Rats of (S)-M1 and Compound 435(S) after Oral and Intravenous Dosing

(S)-M1 and Compound 435(S) (a deuterated form of (S)-M1) were separately dissolved in saline at a concentration of 10 mg/mL. A 1:1 mixture of the two compounds was then prepared containing a final concentration of 5 mg/mL of each compound, which was used for intravenous administration. For oral administration the mixture was further diluted in saline to a final concentration of 1 mg/mL for each compound.

Three male Sprague-Dawley rats were used in each of the oral and intravenous studies. Animals were fasted overnight prior to administration of compounds. Intravenous administration was achieved by bolus injection of a single 5 mg/kg dose of the 1:1 combination into the cannulated jugular vein of the rats. Cannulation was achieved the day prior to dosing on rats that had been placed under anesthesia using ketamine (1M 30 mg/kg). Oral administration was achieved by oral gavage of a single 5 mg/kg dose. Blood samples (250 μL) were collected from the dosed rats at various times post-dosing (2 min, 5 min, 10 min, 20 min, 30 min, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr) by retro-orbital sampling of the rats temporarily anesthetized with isoflurane. Blood samples were placed in tubes containing K2-EDTA and stored on ice until centrifuged. Within 30 minutes of collection, plasma was isolated by centrifugation. A 100-μL aliquot was removed, mixed with 200 μL of acetonitrile and stored at −20°C until further analysis by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer.

Samples were analyzed for the presence of the administered compound, the corresponding ketone (pentoxifylline and Compound 409) and the corresponding M5 metabolite. Samples (10 μL) were injected into a Zorbax SB-C8 (Rapid Resolution) column (2.1 x 30 mm, 3.5 μm). The initial mobile phase condition was 100% A (10 mM ammonium acetate in water) and 0% B (methanol) with a flow rate at 0.5 mL/min. Resolution) column (2.1 x 30 mm, 3.5 pm). The initial mobile 4o phase condition was 100% A (10 mM ammonium acetate in water) and 0% B (methanol) with a flow rate at 0.5 mL/min. For 45 5o counterpart (S)-M1. Because there is a significant serum difference observed between the deuterated and non-deuterated species, the internal standard for the analysis was indipront.

The results of the oral administration in rats are shown in Table 12. The deuterated Compound 435(S) demonstrated a significantly higher AUCo and Cmax than its undeuterated counterpart (S)-M1. Because there is a significant serum interconversion between (S)-M1 and pentoxifylline and both species are therapeutically active, we also quantitated AUCo and Cmax for (S)-M1 together with pentoxifylline, and for Compound 435(S) together with Compound 409. Compound 435(S) together with Compound 409 demonstrated a significantly higher AUCo and Cmax than did (S)-M1 together with pentoxifylline after the oral administration of (S)-M1 and 435(S) respectively.

The AUCo was also measured for the M-5 and M5a metabolites arising from the oral administration of (S)-M1 and 435(S), respectively. The M-5 metabolite may be associated with toxicity in certain patients and is considered undesirable. Table 12 shows that oral administration of Compound 435(S) provides considerably less M5a compared to the level of M5 obtained after administration of non-deuterated (S)-M1. The ratio of active species to M5 metabolite was much more favorable for the deuterated compounds than for the

<table>
<thead>
<tr>
<th>Compound(s) Measured</th>
<th>AUCo (hr*ng/mL)</th>
<th>Cmax (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>435(S)</td>
<td>450 ± 1015</td>
<td>4105 ± 964</td>
</tr>
<tr>
<td>(S)-M1</td>
<td>1628 ± 272</td>
<td>1970 ± 249</td>
</tr>
<tr>
<td>% Difference9</td>
<td>+177%</td>
<td>+162%</td>
</tr>
<tr>
<td>435(S) + 409</td>
<td>13404 ± 3582</td>
<td>15647 ± 742</td>
</tr>
<tr>
<td>(S)-M1 + pentoxifylline</td>
<td>4632 ± 437</td>
<td>5032 ± 630</td>
</tr>
<tr>
<td>% Difference9</td>
<td>+191%</td>
<td>+212%</td>
</tr>
<tr>
<td>Deuterated M5 (M5a)</td>
<td>1924 ± 183</td>
<td>2985 ± 401</td>
</tr>
<tr>
<td>% Difference9</td>
<td>+30%</td>
<td></td>
</tr>
</tbody>
</table>

9 Mass observed via LC-MS/MS. Stereochemistry presumed to be >95% (S) based on published pentoxifylline metabolite reports.
10 % Difference = ([deuterated species] − [nondeuterated species]) / [nondeuterated species]
non-deuterated compounds. The ratio of Compound 435 (S)+Compound 409) to M5a was 7.0, which was much better than the ratio of 1.6 for (S)-M1 + pentoxifylline to M5.

### Table 13

<table>
<thead>
<tr>
<th>Compound(s) Measured</th>
<th>AUC&lt;sub&gt;0&lt;/sub&gt; (hr*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>435(S)</td>
<td>7127 ± 816</td>
</tr>
<tr>
<td>(S)-M1</td>
<td>3300 ± 302</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+110%</td>
</tr>
<tr>
<td>435(S) + pentoxifylline</td>
<td>11247 ± 1326</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+79%</td>
</tr>
<tr>
<td>Deuterated M5 (M5a)</td>
<td>1522 ± 530</td>
</tr>
<tr>
<td>M5</td>
<td>1795 ± 521</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-15%</td>
</tr>
</tbody>
</table>

Table 13 shows the results following intravenous administration in rats. The results for intravenous administration were similar to those for oral administration. Compound 435(S) had an average AUC<sub>0</sub> that was 110% greater than its undeuterated counterpart (S)-M1 after intravenous administration. Compound 435(S) together with Compound 409 had an average AUC<sub>0</sub> that was 79% greater than (S)-M1 together with pentoxifylline after intravenous administration. Intravenous administration of Compound 435(S) provides an amount of M5 metabolite that is 15% less than the amount of M5 metabolite than is provided by intravenous administration of (S)-M1. The ratio of active species to the corresponding M5 metabolite in rats that were intravenously administered Compound 435(S) was 7.4 as compared to 3.5 for rats that were intravenously administered (S)-M1.

### Example 38

**Pharmacokinetic Study of Pentoxifylline and Compound 435(S) in Chimps after Oral and Intravenous Dosing**

Pentoxifylline and Compound 435(S) were separately dissolved in warm (65° C) saline at a concentration of 10 mg/mL. A 1:1 mixture of the two compounds was then prepared containing a final concentration of 5 mg/mL of each compound and the mixture was then sterile filtered through a 0.2-μm filter.

Two chimps (one male and one female) were used in each of the oral and intravenous studies. Animals were fasted overnight prior to administration of compounds. All animals were sedated with ketamine (approximately 10 mg/kg) and/or telazol (approximately 5 mg/kg) prior to dosing. Intravenous administration was achieved by IV infusion of 75 mg of each compound (15 mL total dosing solution) over 10 minutes. Oral administration was achieved by oral gavage of a single 75 mg dose of each compound (15 mL total dosing solution). Blood samples (6 mL) were collected from the dosed chimps at various times prior to and after dosing. For intravenous administrations blood samples were collected at 0 min (pre-infusion), 5 min, 9.5 min (immediately before the end of the infusion), then 6, 15, 30 and 45 min, and 1, 2, 4, 6, 8, 10 and 12 hr after the infusion is stopped. For oral administrations, blood samples were collected at 0 min (pre dose), 15 and 30 min, and 1, 1.5, 2, 4, 6, 8, 10 and 12 hr post dose.

### Table 14

<table>
<thead>
<tr>
<th>Compound(s) Measured&lt;sup&gt;ab&lt;/sup&gt;</th>
<th>AUC&lt;sub&gt;0&lt;/sub&gt; (hr*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>435(S)</td>
<td>829 ± 672</td>
</tr>
<tr>
<td>(S)-M1</td>
<td>300 ± 301</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+176% (+123%)</td>
</tr>
<tr>
<td>435(S) + 409</td>
<td>1877 ± 1277</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+165% (+143%)</td>
</tr>
<tr>
<td>Deuterated M5 (M5a)</td>
<td>462 ± 696</td>
</tr>
<tr>
<td>M5</td>
<td>1906 ± 688</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-68% (-68%)</td>
</tr>
</tbody>
</table>

Table 14 shows the results of oral administration of 435(S) and pentoxifylline in chimps. Following oral administration of a 1:1 combination of Compound 435(S) and pentoxifylline, both Compound 435(S) and its corresponding ketone Compound 409 demonstrated significantly higher average AUC<sub>0</sub> values than the corresponding undeuterated counterparts, (S)-M1 and pentoxifylline. The average AUC<sub>0</sub> for Compound 435(S) together with Compound 409 was significantly higher than the average AUC<sub>0</sub> for (S)-M1 together with pentoxifylline. In addition, the average AUC<sub>0</sub> for the undesired deuterated M-5 metabolite (M5a) was significantly lower than that of the undeuterated M-5. Finally, the ratio of average of active species to M5 metabolite for the deuterated compounds ((435(S)+409):(deuterated M5)) was approximately 8-fold higher than the corresponding ratio for the undeuterated species ((S)-M1 +pentoxifylline):M5).

### Table 15

<table>
<thead>
<tr>
<th>Compound(s) Measured&lt;sup&gt;ab&lt;/sup&gt;</th>
<th>AUC&lt;sub&gt;0&lt;/sub&gt; (hr*ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>435(S)</td>
<td>2522 ± 1213</td>
</tr>
<tr>
<td>(S)-M1</td>
<td>1559 ± 657</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+61% (+84%)</td>
</tr>
<tr>
<td>435(S) + 409</td>
<td>3219 ± 1607</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+40% (+57%)</td>
</tr>
<tr>
<td>Deuterated M5</td>
<td>428 ± 632</td>
</tr>
<tr>
<td>M5</td>
<td>1195 ± 1560</td>
</tr>
<tr>
<td>% Difference&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-65% (-60%)</td>
</tr>
</tbody>
</table>

Table 15 shows the results of intravenous administration of 435(S) and pentoxifylline in chimps. The results following intravenous administration showed favorable differentiation of the deuterated compounds, though not as pronounced as...
AUC0-12 ketone Compound 409 demonstrated significantly higher
published pentoxifylline metab0
aMass observed via LC-MS/MS. Stereochemistry presumed to be >95% (S) based on
two compounds was not sterile filtered; and (c) oral admin- 25
which may be associated with intolerability in renally-im-
pounds. Moreover, deuterium substitution in the present com-
provide significantly greater plasma exposure of desired
metabolite produced decreased by between 60 and 65%. The 5
were between 40 and 57% higher, while the amounts of M5
administration of pentoxifylline, the amounts of active spe-
metabolite to M5 metabolite in chimps that were
intravenously administered Compound 435(S) was approxi-
mately 4-fold higher than in chimps administered pentoxifyl-
line. The above results show that compounds of this invention
provide significantly greater plasma exposure of desired
active species than the corresponding non-deuterated com-
ounds was shown to reduce levels of the M5 metabolite,
ies produced from the administration of Compound 435(S)
intravenously administered Compound 435(S) was approxi-
mately 4-fold higher than in chimps administered pentoxifyl-
line.

**Example 39**

**Pharmacokinetic Study of Pentoxifylline and Compound 435(S) in Chimps after Oral Dosing**

Pentoxifylline and Compound 435(S) were tested according
to a protocol similar to the Oral Dosing protocol followed in Example 38, except that (a) the compounds were separately
dissolved in water rather than saline; (b) the mixture of the
two compounds was not sterile filtered; and (c) oral admin-
istration was achieved by oral gavage of a single 65 mg dose
of each compound (13 mL total dosing solution).

**TABLE 16**

<table>
<thead>
<tr>
<th>Compound(s) Measured°</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>435(S)</td>
<td>214</td>
<td>183</td>
</tr>
<tr>
<td>(S)-M1</td>
<td>75</td>
<td>88</td>
</tr>
<tr>
<td>% Differenceb</td>
<td>+185%</td>
<td>+108%</td>
</tr>
<tr>
<td>435(S) + 409</td>
<td>344</td>
<td>262</td>
</tr>
<tr>
<td>(S)-M1 + pentoxifylline</td>
<td>137</td>
<td>127</td>
</tr>
<tr>
<td>% Differencec</td>
<td>+151%</td>
<td>+108%</td>
</tr>
<tr>
<td>Deuterated M5 (M5a)</td>
<td>667</td>
<td>609</td>
</tr>
<tr>
<td>M5</td>
<td>817</td>
<td>811</td>
</tr>
<tr>
<td>% Differencec</td>
<td>-18%</td>
<td>-23%</td>
</tr>
</tbody>
</table>

°Mass observed via LC-MS/MS. Stereochemistry presumed to be ≥95% (S) based on
published pentoxifylline metabolism reports.

b% Difference = \[(deuterated species) - (nondeuterated species)\](100)/(nondeuterated spe-
cies)

d% Difference = \[(deuterated species) - (nondeuterated species)\](100)/(nondeuterated spe-
cies)

Table 16 shows the results of oral administration of 435(S) and pentoxifylline in chimps. Similarly to what was shown in Table 14, both Compound 435(S) and its corresponding ketone Compound 409 demonstrated significantly higher average AUC0-12 values than the corresponding undeuterated counterparts, (S)-M1 and pentoxifylline, where AUC0-12 refers to the area under the curve for the 0- to 12-hour period. The average AUC0-12 for Compound 435(S) together with Compound 409 was significantly higher than the average AUC0-12 for (S)-M1 together with pentoxifylline.

The average AUC0-12 for the deuterated M-5 metabolite (M5a) was significantly lower than that of the undeuterated M-5.

**Example 40**

**Pharmacokinetic Study of 435(S) and Other Representative Compounds in Chimps after Oral Dosing**

435(S) and representative compounds 121(S), 137(S), 421(S) and 437(S) were separately dissolved in warm (65°

C.) water at a concentration [(of 10 mg/mL)]. The same
protocol described for Example 39 was then followed for each representative compound.

**TABLE 17**

<table>
<thead>
<tr>
<th>Compound(s) Measured°</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>435(S)</td>
<td>354</td>
<td>133</td>
</tr>
<tr>
<td>121(S)</td>
<td>304</td>
<td>165</td>
</tr>
<tr>
<td>435(S) + 409</td>
<td>715</td>
<td>281</td>
</tr>
<tr>
<td>121(S) + 107</td>
<td>553</td>
<td>224</td>
</tr>
<tr>
<td>Deuterated M5 (M5a)</td>
<td>585</td>
<td>670</td>
</tr>
<tr>
<td>M5</td>
<td>630</td>
<td>653</td>
</tr>
<tr>
<td>137(S)</td>
<td>435</td>
<td></td>
</tr>
<tr>
<td>334</td>
<td>137(S) + 409</td>
<td>127</td>
</tr>
<tr>
<td>Deuterated M5 (M5a)</td>
<td>719</td>
<td>754</td>
</tr>
<tr>
<td>M5</td>
<td>539</td>
<td>635</td>
</tr>
<tr>
<td>421(S)</td>
<td>834</td>
<td></td>
</tr>
<tr>
<td>306</td>
<td>421(S) + 407</td>
<td>979</td>
</tr>
<tr>
<td>Deuterated M5 (M5a)</td>
<td>500</td>
<td>376</td>
</tr>
<tr>
<td>M5</td>
<td>447</td>
<td>350</td>
</tr>
<tr>
<td>435(S)</td>
<td>1140</td>
<td></td>
</tr>
<tr>
<td>367</td>
<td>435(S) + 409</td>
<td>876</td>
</tr>
<tr>
<td>37(S) + 407</td>
<td>947</td>
<td>1662</td>
</tr>
<tr>
<td>Deuterated M5 (M5a)</td>
<td>562</td>
<td>306</td>
</tr>
<tr>
<td>Deuterated M5 (M5b)</td>
<td>627</td>
<td>416</td>
</tr>
</tbody>
</table>

°Mass observed via LC-MS/MS.
the present invention and practice the claimed methods. It should be understood that the foregoing discussion and examples merely present a detailed description of certain preferred embodiments. It will be apparent to those of ordinary skill in the art that various modifications and equivalents can be made without departing from the spirit and scope of the invention.

What is claimed is:
1. A compound of Formula C:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein $R^1$ is selected from $-CH_3$ and $-CD_3$; $R^2$ is selected from $-CH_3$ and $-CD_3$; $Y^1$ is hydrogen, wherein the isotopic enrichment factor for each designated deuterium atom is at least 5000.

2. The compound of claim 1, wherein $R^1$ is $-CH_3$.
3. The compound of claim 1, wherein $R^2$ is $-CD_3$.
4. The compound of claim 1 wherein $R^2$ is $-CH_3$.
5. The compound of claim 1 wherein $R^2$ is $-CD_3$.
6. The compound of claim 1, wherein $R^1$ is $-CH_3$ and $R^2$ is $-CD_3$.
7. The compound of claim 1, wherein the compound is selected from the group consisting of the following compounds

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof.

8. A compound of Formula D:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein $R^1$ is $-CH_3$; $R^2$ is selected from $-CH_3$ and $-CD_3$; $Y^1$ is hydrogen; wherein the isotopic enrichment factor for each designated deuterium atom is at least 5000.

9. The compound of claim 8, wherein $R^2$ is $-CH_3$.
10. The compound of claim 8, wherein $R^2$ is $-CD_3$.
11. The compound of claim 8, wherein the compound is represented by the following structural formula:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

13. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

14. A compound of the following formula:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein the isotopic enrichment factor for each designated deuterium atom is at least 5000.

15. The compound of claim 14, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

16. The compound of claim 8, wherein any atom not designated as deuterium is present at its natural isotopic abundance.

17. The compound of claim 12, wherein isotopic enrichment factor for each designated deuterium atom is at least 6000.

18. The compound of claim 12, wherein isotopic enrichment factor for each designated deuterium atom is at least 6600.

19. The compound of claim 15, wherein isotopic enrichment factor for each designated deuterium atom is at least 6000.

20. The compound of claim 15, wherein isotopic enrichment factor for each designated deuterium atom is at least 6600.

21. The compound of claim 16, wherein isotopic enrichment factor for each designated deuterium atom is at least 6600.
22. The compound of claim 16, wherein isotopic enrichment factor for each designated deuterium atom is at least 6600.

23. The compound of claim 1, wherein the compound comprises less than 10% of the other stereoisomer.

24. The compound of claim 15, wherein the compound comprises less than 10% of the other stereoisomer.

25. The compound of claim 21, wherein the compound comprises less than 10% of the other stereoisomer.

26. The compound of claim 15, wherein the compound comprises less than 5% of the other stereoisomer.

27. The compound of claim 21, wherein the compound comprises less than 5% of the other stereoisomer.

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