



US009328113B2

(12) **United States Patent**
Tung et al.

(10) **Patent No.:** **US 9,328,113 B2**
(45) **Date of Patent:** **May 3, 2016**

(54) **SUBSTITUTED XANTHINE DERIVATIVES**

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/391,443**

(22) PCT Filed: **Apr. 12, 2013**

(86) PCT No.: **PCT/US2013/036454**

§ 371 (c)(1),

(2) Date: **Oct. 9, 2014**

(87) PCT Pub. No.: **WO2013/155465**

PCT Pub. Date: **Oct. 17, 2013**

(65) **Prior Publication Data**

US 2015/0119407 A1 Apr. 30, 2015

Related U.S. Application Data

(60) Provisional application No. 61/623,858, filed on Apr.
13, 2012.

(51) **Int. Cl.**

C07D 473/10 (2006.01)

C07D 487/04 (2006.01)

(52) **U.S. Cl.**

CPC **C07D 473/10** (2013.01); **C07D 487/04**
(2013.01); **C07B 2200/05** (2013.01)

(58) **Field of Classification Search**

CPC **C07D 473/10**; **C07B 2200/05**
See application file for complete search history.

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(57) **ABSTRACT**

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 derivatives of pentifylline. 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 pentifylline and related compounds are beneficial.

9 Claims, No Drawings

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SUBSTITUTED XANTHINE DERIVATIVES

RELATED APPLICATIONS

This application is a 35 U.S.C. §371 national stage filing of International Application No. PCT/US2013/036454, filed Apr. 12, 2013, which claims the benefit of U.S. Provisional Application No. 61/623,858, filed Apr. 13, 2012, the entire teachings of each of which 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, 64:367-91; 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 deuteration caused 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).

The effects of deuterium modification on a drug's metabolic properties are not predictable even when deuterium atoms are incorporated at known sites of metabolism. Only by actually preparing and testing a deuterated drug can one determine if and how the rate of metabolism will differ from that of its undeuterated counterpart. Many drugs have multiple sites where metabolism is possible. The site(s) where deuterium substitution is required and the extent of deuteration necessary to see an effect on metabolism, if any, will be different for each drug.

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 pentifylline. 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 pentifylline and related compounds are beneficial.

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 (e.g., a disease or disorder delineated herein), lessen the severity of the disease or improve the symptoms associated with the disease.

"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 pentifylline will inherently contain small amounts of deuterated isotopologues. The concentration of naturally abundant stable hydrogen and carbon isotopes, notwithstanding this variation, is small and immaterial 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; Gannes 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), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

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 molecules. 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-toluenesulfonic acid, salicylic acid, tartaric acid, bitartaric acid, ascorbic acid, maleic acid, besylic acid,

fumaric acid, gluconic acid, glucuronic 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, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephthalate, sulfonate, xylene sulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, β -hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-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.

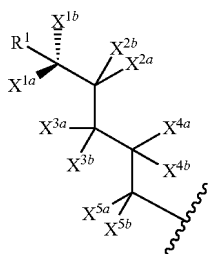
"The term 'alkyl' refers to a monovalent saturated hydrocarbon group. C₁-C₆ alkyl is an alkyl having from 1 to 6 carbon atoms. An alkyl may be linear or branched. Examples of alkyl groups include methyl; ethyl; propyl, including n-propyl and isopropyl; butyl, including n-butyl, isobutyl, sec-butyl, and t-butyl; pentyl, including, for example, n-pentyl, isopentyl, and neopentyl; and hexyl, including, for example, n-hexyl and 2-methylpentyl.

It is understood that the carbon atom that bears substituents X^{1a} and X^{1b}; X^{2a} and X^{2b}; X^{3a} and X^{3b}; X^{4a} and X^{4b}; and X^{5a} and X^{5b} in Formulae A, B, B-I, B-II and E can be chiral in some instances (when X^{1a} and X^{1b} are different from each other; when X^{2a} and X^{2b} are different from each other; when X^{3a} and X^{3b} are different from each other; X^{4a} and X^{4b} are different from each other; and when X^{5a} and X^{5b} are different from each other; and in other instances it can be achiral (when X^{1a} and X^{1b} are the same; when X^{2a} and X^{2b} are the same; when X^{3a} and X^{3b} are the same; when X^{4a} and X^{4b} are the same; and when X^{5a} and X^{5b} are the same. As such, chiral compounds of this invention can exist as either individual enantiomers, or as racemic or scalemic mixtures of enantiomers. Accordingly, a compound of the present invention will include racemic and scalemic 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

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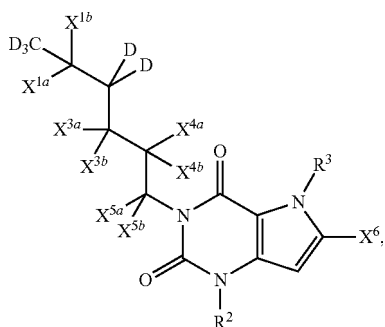
deuterium. In one example of this aspect, R^1 is CH_3 . In another example of this aspect, R^1 is CD_3 . In one more particular example of this aspect, R^1 is CD_3 and X^{2a} and X^{2b} are each hydrogen. In one example of this aspect, R^2 is CH_3 . In another example of this aspect, R^2 is CD_3 . In one example of this aspect, R^3 is CH_3 . In another example of this aspect, R^3 is CD_3 . In one example of this aspect, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is hydrogen. In another example of this aspect, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is deuterium. In another example of this aspect, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen. In another example of this aspect, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is deuterium.

In another aspect of the embodiment where X^{1a} is deuterium and X^{1b} is hydrogen, the carbon bearing X^{1a} and X^{1b} has the following stereochemistry:



In one example of this aspect, X^{2a} and X^{2b} are each hydrogen. In another example of this aspect, X^{2a} and X^{2b} are each deuterium. In one example of this aspect, R^1 is CH_3 . In another example of this aspect, R^1 is CD_3 . In one more particular example of this aspect, R^1 is CD_3 and X^{2a} and X^{2b} are each hydrogen. In one example of this aspect, R^2 is CH_3 . In another example of this aspect, R^2 is CD_3 . In one example of this aspect, R^3 is CH_3 . In another example of this aspect, R^3 is CD_3 . In one example of this aspect, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is hydrogen. In another example of this aspect, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is deuterium. In another example of this aspect, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen. In another example of this aspect, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is deuterium.

One embodiment of the compound of Formula A provides a compound of Formula B:



Formula B

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or a pharmaceutically acceptable salt thereof, wherein each of R^3 and R^2 is independently selected from $-CH_3$ and $-CD_3$; X^{3a} and X^{3b} are each hydrogen or each deuterium; X^{4a} and X^{4b} are each hydrogen or each deuterium; X^{5a} and X^{5b} are each hydrogen or each deuterium; X^6 is hydrogen or deuterium; and either (a) X^{1a} is deuterium and X^{1b} is hydrogen, or (b) X^{1a} and X^{1b} are each hydrogen or each deuterium

One embodiment provides a compound of Formula B, wherein each X^3 , each X^4 and each X^5 is hydrogen. In one aspect, R^3 and R^2 are each $-CD_3$. In one aspect X^6 is deuterium. In one aspect X^6 is hydrogen.

Another embodiment provides a compound of Formula B, wherein each X^3 , each X^4 and each X^5 is deuterium. In one aspect, R^3 and R^2 are each $-CD_3$. In one aspect X^6 is deuterium. In another aspect X^6 is hydrogen.

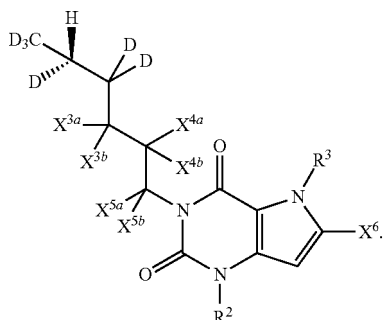
Yet another embodiment provides a compound of Formula B, wherein at least one of R^3 and R^2 is $-CD_3$. In one aspect, R^3 is $-CH_3$ and R^2 is $-CD_3$. In one aspect, R^2 is $-CH_3$ and R^3 is $-CD_3$. In one aspect, R^3 and R^2 are each $-CD_3$. In one aspect, X^6 is deuterium. In another aspect, X^6 is hydrogen. In one aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is deuterium. In another aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is hydrogen.

In one embodiment of the compound of Formula B, X^{1a} and X^{1b} are each hydrogen or each deuterium. In one aspect of this embodiment, each X^3 , each X^4 and each X^5 is hydrogen. In one example of this aspect, R^3 and R^2 are each $-CD_3$. In one example of this aspect X^6 is deuterium. In another example of this aspect X^6 is hydrogen. In another aspect of this embodiment, each X^3 , each X^4 and each X^5 is deuterium. In one example of this aspect, R^3 and R^2 are each $-CD_3$. In one example of this aspect X^6 is deuterium. In another example of this aspect X^6 is hydrogen. In one aspect of this embodiment, R^3 and R^2 are each $-CH_3$. In one aspect of this embodiment, at least one of R^3 and R^2 is each $-CD_3$. In one example of this aspect, R^3 is $-CH_3$ and R^2 is $-CD_3$. In one example of this aspect, R^2 is $-CH_3$ and R^3 is $-CD_3$. In one example of this aspect, R^3 and R^2 are each $-CD_3$. In one example of this aspect, X^6 is deuterium. In another example of this aspect, X^6 is hydrogen. In one example of this aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is deuterium. In another example of this aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is hydrogen.

In one embodiment of the compound of Formula B, X^{1a} is deuterium and X^{1b} is hydrogen. In one aspect of this embodiment, each X^3 , each X^4 and each X^5 is hydrogen. In one example of this aspect, R^3 and R^2 are each $-CD_3$. In one example of this aspect X^6 is deuterium. In another example of this aspect X^6 is hydrogen. In another aspect of this embodiment, each X^3 , each X^4 and each X^5 is deuterium. In one example of this aspect, R^3 and R^2 are each $-CD_3$. In one example of this aspect X^6 is deuterium. In another example of this aspect X^6 is hydrogen. In one aspect of this embodiment, R^3 and R^2 are each $-CH_3$. In one aspect of this embodiment, at least one of R^3 and R^2 is each $-CD_3$. In one example of this aspect, R^3 is $-CH_3$ and R^2 is $-CD_3$. In one example of this aspect, R^2 is $-CH_3$ and R^3 is $-CD_3$. In one example of this aspect, R^3 and R^2 are each $-CD_3$. In one example of this aspect, X^6 is deuterium. In another example of this aspect, X^6 is hydrogen. In one example of this aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is deuterium. In another example of this aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is hydrogen.

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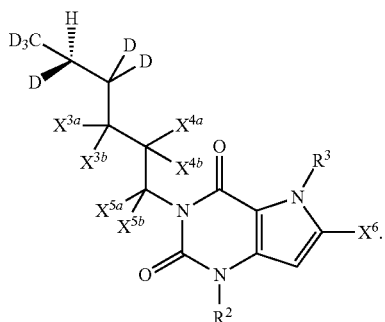
In one embodiment of the compound of Formula B, the compound has the Formula B-I:



Formula B-I

In one aspect of this embodiment, each X^3 , each X^4 and each X^5 is hydrogen. In one example of this aspect, R^3 and R^2 are each $-\text{CD}_3$. In one example of this aspect X^6 is deuterium. In another example of this aspect X^6 is hydrogen. In another aspect of this embodiment, each X^3 , each X^4 and each X^5 is deuterium. In one example of this aspect, R^3 and R^2 are each $-\text{CD}_3$. In one example of this aspect X^6 is deuterium. In another example of this aspect X^6 is hydrogen. In one aspect of this embodiment, R^3 and R^2 are each $-\text{CH}_3$. In one aspect of this embodiment, at least one of R^3 and R^2 is each $-\text{CD}_3$. In one example of this aspect, R^3 is $-\text{CH}_3$ and R^2 is $-\text{CD}_3$. In one example of this aspect, R^2 is $-\text{CH}_3$ and R^3 is $-\text{CD}_3$. In one example of this aspect, R^3 and R^2 are each $-\text{CD}_3$. In one example of this aspect, X^6 is deuterium. In another example of this aspect, X^6 is hydrogen. In one example of this aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is deuterium. In another example of this aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is hydrogen.

In one embodiment of the compound of Formula B, the compound has the Formula B-II:



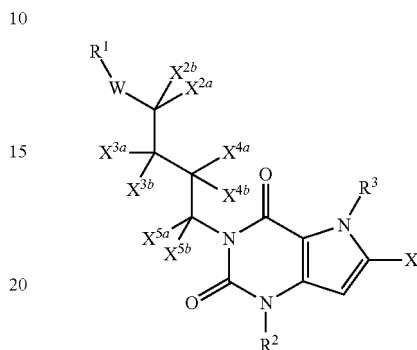
Formula B-II

In one aspect of this embodiment, each X^3 , each X^4 and each X^5 is hydrogen. In one example of this aspect, R^3 and R^2 are each $-\text{CD}_3$. In one example of this aspect X^6 is deuterium. In another example of this aspect X^6 is hydrogen. In another aspect of this embodiment, each X^3 , each X^4 and each X^5 is deuterium. In one example of this aspect, R^3 and R^2 are each $-\text{CD}_3$. In one example of this aspect X^6 is deuterium. In another example of this aspect X^6 is hydrogen. In one aspect of this embodiment, R^3 and R^2 are each $-\text{CH}_3$. In one aspect of this embodiment, at least one of R^3 and R^2 is each $-\text{CD}_3$. In one example of this aspect, R^3 is $-\text{CH}_3$ and R^2 is $-\text{CD}_3$. In one example of this aspect, R^2 is $-\text{CH}_3$ and R^3 is $-\text{CD}_3$.

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In one example of this aspect, R^3 and R^2 are each $-\text{CD}_3$. In one example of this aspect, X^6 is deuterium. In another example of this aspect, X^6 is hydrogen. In one example of this aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is deuterium. In another example of this aspect, each X^3 , each X^4 and each X^5 is hydrogen and X^6 is hydrogen.

The present invention in one embodiment provides a compound of Formula E:



or pharmaceutically acceptable salts thereof, wherein

W is O, S, S(O), S(O)₂, NH, or NC₁₋₆ alkyl; each of X^{2a} , X^{2b} , X^{3a} , X^{3b} , X^{4a} , X^{4b} , X^{5a} , X^{5b} and X^6 is independently hydrogen or deuterium; and each of R^1 , R^2 , and R^3 , is independently CH₃ or CD₃; with the proviso that if each X is hydrogen, then at least one R is CD₃.

In one embodiment of the compound of Formula A, X^{3a} and X^{3b} are each hydrogen or each deuterium.

In one embodiment of the compound of Formula A, X^{4a} and X^{4b} are each hydrogen or each deuterium.

In one embodiment of the compound of Formula A, X^{5a} and X^{5b} are each hydrogen or each deuterium.

In one embodiment of the compound of Formula A, X^6 is hydrogen. In another embodiment, X^6 is deuterium.

In the embodiment of Formula A wherein X^6 is hydrogen, in one aspect each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is hydrogen. In another aspect, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is deuterium. In another aspect, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen. In another aspect, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is deuterium.

In one embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is hydrogen.

In one embodiment, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is deuterium.

In one embodiment, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen.

In one embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is deuterium.

In one embodiment of the compound of Formula E, X^{2a} and X^{2b} are each hydrogen. In another embodiment, X^{2a} and X^{2b} are each deuterium. In one aspect of these embodiments, R^1 is CH₃. In one aspect of these embodiments, W is O. In another aspect of these embodiments, W is S. In another aspect of these embodiments, W is NH. In another aspect of these embodiments, W is N—C₁₋₆ alkyl. In one aspect of these embodiments, R^2 is CH₃. In another aspect of these embodiments, R^2 is CD₃. In one aspect of these embodiments, R^3 is CH₃. In another aspect of these embodiments, R^3 is CD₃. In one aspect of these embodiments, each X^3 is deuterium.

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terium; each X^4 is deuterium; and each X^5 is deuterium. In another aspect, each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen.

In one embodiment of the compound of Formula E, W is O. In one aspect of this embodiment, X^{2a} and X^{2b} are each hydrogen. In another aspect of this embodiment, X^{2a} and X^{2b} are each deuterium. In one aspect of this embodiment, R^1 is CH_3 . In another aspect of this embodiment, R^1 is CD_3 . In one example of this aspect, X^{2a} and X^{2b} are each hydrogen. In one aspect of this embodiment, R^2 is CH_3 . In another aspect of this embodiment, R^2 is CD_3 . In one aspect of this embodiment, R^3 is CH_3 . In another aspect of this embodiment, R^3 is CD_3 . In one aspect of this embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is hydrogen. In another aspect, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is deuterium. In another aspect, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen. In another aspect, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is deuterium.

In one embodiment, W is S, S(O) or S(O)₂. In one aspect of this embodiment, X^{2a} and X^{2b} are each hydrogen. In another aspect of this embodiment, X^{2a} and X^{2b} are each deuterium. In one aspect of this embodiment, R^1 is CH_3 . In another aspect of this embodiment, R^1 is CD_3 . In one example of this aspect, X^{2a} and X^{2b} are each hydrogen. In one aspect of this embodiment, R^2 is CH_3 . In another aspect of this embodiment, R^2 is CD_3 . In one aspect of this embodiment, R^3 is CH_3 . In another aspect of this embodiment, R^3 is CD_3 . In one aspect of this embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is hydrogen. In another aspect of this embodiment, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is deuterium. In another aspect of this embodiment, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen. In another aspect of this embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is deuterium.

In one embodiment, W is NH. In one aspect of this embodiment, X^{2a} and X^{2b} are each hydrogen. In another aspect of this embodiment, X^{2a} and X^{2b} are each deuterium. In one aspect of this embodiment, R^1 is CH_3 . In another aspect of this embodiment, R^1 is CD_3 . In one example of this aspect, X^{2a} and X^{2b} are each hydrogen. In one aspect of this embodiment, R^2 is CH_3 . In another aspect of this embodiment, R^2 is CD_3 . In one aspect of this embodiment, R^3 is CH_3 . In another aspect of this embodiment, R^3 is CD_3 . In one aspect of this embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is hydrogen. In another aspect of this embodiment, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is deuterium. In another aspect of this embodiment, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen. In another aspect of this embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is deuterium.

In one embodiment, W is NC_1-C_6 alkyl, where the C_1-C_6 alkyl may be, for example, CH_3 , C_2H_5 , $n-C_3H_7$, $i-C_3H_7$, $n-C_4H_9$, $sec-C_4H_9$, $i-C_4H_9$ or $t-C_4H_9$. In one aspect of this embodiment, X^{2a} and X^{2b} are each hydrogen. In another aspect of this embodiment, X^{2a} and X^{2b} are each deuterium. In one aspect of this embodiment, R^1 is CH_3 . In another aspect of this embodiment, R^1 is CD_3 . In one example of this aspect, X^{2a} and X^{2b} are each hydrogen. In one aspect of this embodiment, R^2 is CH_3 . In another aspect of this embodiment, R^2 is CD_3 . In one aspect of this embodiment, R^3 is CH_3 . In another aspect of this embodiment, R^3 is CD_3 . In one aspect of this embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is hydrogen. In another aspect of this embodiment, each X^2 is deuterium; each X^3 is deuterium;

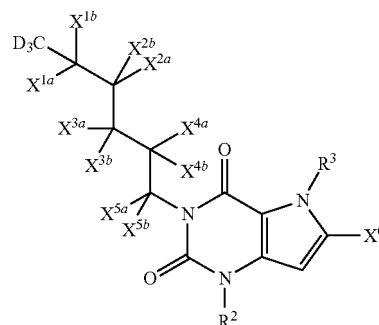
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each X^4 is deuterium; and each X^5 is deuterium. In another aspect of this embodiment, each X^2 is deuterium; each X^3 is deuterium; each X^4 is deuterium; and each X^5 is hydrogen. In another aspect of this embodiment, each X^2 is hydrogen; each X^3 is hydrogen; each X^4 is hydrogen; and each X^5 is deuterium.

In one embodiment of the compound of Formula A, the compound is a compound selected from the group consisting of the compounds of Table 1:

TABLE 1

Cmpd	$X^{1a} =$	$X^{2a} =$	$X^{3a} =$	$X^{4a} =$	$X^{5a} =$	X^6	R^1	R^2	R^3
	X^{1b}	X^{2b}	X^{3b}	X^{4b}	X^{5b}				
100	D	D	D	D	D	H	CD_3	CD_3	CD_3
101	D	D	D	D	D	H	CD_3	CH_3	CH_3
102	D	D	H	H	H	H	CD_3	CH_3	CH_3
103	D	D	H	H	H	H	CD_3	CD_3	CD_3
104	H	D	H	H	H	H	CD_3	CH_3	CH_3
105	H	D	H	H	H	H	CD_3	CD_3	CD_3
106	D	H	H	H	H	H	CH_3	CD_3	CD_3
107	D	H	H	H	H	H	CH_3	CH_3	CH_3
108	D	D	D	D	D	H	CD_3	CD_3	CH_3
109	D	D	D	D	D	H	CD_3	CH_3	CD_3
110	D	D	H	H	H	H	CD_3	CH_3	CD_3
111	D	D	H	H	H	H	CD_3	CD_3	CH_3
112	H	D	H	H	H	H	CD_3	CH_3	CD_3
113	H	D	H	H	H	H	CD_3	CD_3	CH_3
114	D	H	H	H	H	H	CH_3	CD_3	CH_3
115	D	H	H	H	H	H	CH_3	CH_3	CD_3
116	H	H	H	H	H	H	CH_3	CD_3	CD_3



or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of Formula E, the compound is a compound selected from the group consisting of the compounds of Table 2, wherein W is O:

TABLE 2

Cmpd	$X^{2a} =$	$X^{3a} =$	$X^{4a} =$	$X^{5a} =$	X^6	R^1	R^2	R^3
	X^{2b}	X^{3b}	X^{4b}	X^{5b}				
200	D	D	D	D	H	CD_3	CD_3	CD_3
201	D	D	D	D	H	CD_3	CH_3	CH_3
202	D	H	H	H	H	CD_3	CH_3	CH_3
203	D	H	H	H	H	CD_3	CD_3	CD_3
206	H	H	H	H	H	CH_3	CD_3	CD_3
207	H	H	H	H	H	CH_3	CH_3	CH_3
208	D	D	D	D	H	CD_3	CD_3	CH_3
209	D	D	D	D	H	CD_3	CH_3	CD_3
210	D	H	H	H	H	CD_3	CH_3	CD_3
211	D	H	H	H	H	CD_3	CD_3	CH_3
214	H	H	H	H	H	CH_3	CD_3	CH_3
215	H	H	H	H	H	CH_3	CH_3	CD_3

or a pharmaceutically acceptable salt thereof.

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In one embodiment of the compound of Formula E, the compound is a compound selected from the group consisting of the compounds of Table 3, wherein W is NH:

TABLE 3

Cmpd	X ^{2a} = X ^{2b}	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	X ⁶	R ¹	R ²	R ³
300	D	D	D	D	H	CD ₃	CD ₃	CD ₃
301	D	D	D	D	H	CD ₃	CH ₃	CH ₃
302	D	H	H	H	H	CD ₃	CH ₃	CH ₃
303	D	H	H	H	H	CD ₃	CD ₃	CD ₃
306	H	H	H	H	H	CH ₃	CD ₃	CD ₃
307	H	H	H	H	H	CH ₃	CH ₃	CH ₃
308	D	D	D	D	H	CD ₃	CD ₃	CH ₃
309	D	D	D	D	H	CD ₃	CH ₃	CD ₃
310	D	H	H	H	H	CD ₃	CH ₃	CD ₃
311	D	H	H	H	H	CD ₃	CD ₃	CH ₃
314	H	H	H	H	H	CH ₃	CD ₃	CH ₃
315	H	H	H	H	H	CH ₃	CH ₃	CD ₃

or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of Formula E, the compound is a compound selected from the group consisting of the compounds of Table 4, wherein W is NCH₃:

TABLE 4

Cmpd	X ^{2a} = X ^{2b}	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	X ⁶	R ¹	R ²	R ³
400	D	D	D	D	H	CD ₃	CD ₃	CD ₃
401	D	D	D	D	H	CD ₃	CH ₃	CH ₃
402	D	H	H	H	H	CD ₃	CH ₃	CH ₃
403	D	H	H	H	H	CD ₃	CD ₃	CD ₃
406	H	H	H	H	H	CH ₃	CD ₃	CD ₃
407	H	H	H	H	H	CH ₃	CH ₃	CH ₃
408	D	D	D	D	H	CD ₃	CD ₃	CH ₃
409	D	D	D	D	H	CD ₃	CH ₃	CD ₃
410	D	H	H	H	H	CD ₃	CH ₃	CD ₃
411	D	H	H	H	H	CD ₃	CD ₃	CH ₃
414	H	H	H	H	H	CH ₃	CD ₃	CH ₃
415	H	H	H	H	H	CH ₃	CH ₃	CD ₃

or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of Formula B, the compound is a compound selected from the group consisting of the compounds of Table 5, wherein each of X^{1a} and X^{1b} is hydrogen and X⁶ is hydrogen:

TABLE 5

Cmpd	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	R ²	R ³
503	H	H	D	CH ₃	CH ₃
504	H	H	D	CH ₃	CD ₃
505	H	H	D	CD ₃	CH ₃
506	H	H	D	CD ₃	CD ₃
507	H	D	H	CH ₃	CH ₃
508	H	D	H	CH ₃	CD ₃
509	H	D	H	CD ₃	CH ₃
510	H	D	H	CD ₃	CD ₃
511	H	D	D	CH ₃	CH ₃
512	H	D	D	CH ₃	CD ₃
513	H	D	D	CD ₃	CH ₃
514	H	D	D	CD ₃	CD ₃
515	D	H	H	CH ₃	CH ₃
516	D	H	H	CH ₃	CD ₃
517	D	H	H	CD ₃	CH ₃
518	D	H	H	CD ₃	CD ₃
519	D	H	D	CH ₃	CH ₃
520	D	H	D	CH ₃	CD ₃
521	D	H	D	CD ₃	CH ₃
522	D	H	D	CD ₃	CD ₃
523	D	D	H	CH ₃	CH ₃

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TABLE 5-continued

Cmpd	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	R ²	R ³	
5	524	D	D	H	CH ₃	CD ₃
	525	D	D	H	CD ₃	CH ₃
	526	D	D	H	CD ₃	CD ₃
	527	D	D	D	CH ₃	CH ₃
	528	D	D	D	CH ₃	CD ₃
	529	D	D	D	CD ₃	CH ₃
10	530	D	D	D	CD ₃	CD ₃

or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of Formula B, the compound is a compound selected from the group consisting of the compounds of Table 6, wherein each of X^{1a} and X^{1b} is deuterium and X⁶ is hydrogen:

TABLE 6

Cmpd	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	R ²	R ³	
20	603	H	H	D	CH ₃	CH ₃
	604	H	H	D	CH ₃	CD ₃
	605	H	H	D	CD ₃	CH ₃
25	606	H	H	D	CD ₃	CD ₃
	607	H	D	H	CH ₃	CH ₃
	608	H	D	H	CH ₃	CD ₃
	609	H	D	H	CD ₃	CH ₃
	610	H	D	H	CD ₃	CD ₃
	611	H	D	D	CH ₃	CH ₃
	612	H	D	D	CH ₃	CD ₃
30	613	H	D	D	CD ₃	CH ₃
	614	H	D	D	CD ₃	CD ₃
	615	D	H	H	CH ₃	CH ₃
	616	D	H	H	CH ₃	CD ₃
	617	D	H	H	CD ₃	CH ₃
	618	D	H	H	CD ₃	CD ₃
35	619	D	H	D	CH ₃	CH ₃
	620	D	H	D	CH ₃	CD ₃
	621	D	H	D	CD ₃	CH ₃
	622	D	H	D	CD ₃	CD ₃
	623	D	D	H	CH ₃	CH ₃
	624	D	D	H	CH ₃	CD ₃
40	625	D	D	H	CD ₃	CH ₃
	626	D	D	H	CD ₃	CD ₃

or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of Formula B-I, the compound is a compound selected from the group consisting of the compounds of Table 7, wherein X⁶ is hydrogen:

TABLE 7

Cmpd	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	R ²	R ³	
50	700	H	H	H	CH ₃	CD ₃
	701	H	H	H	CD ₃	CH ₃
	702	H	H	H	CD ₃	CD ₃
	703	H	H	D	CH ₃	CH ₃
55	704	H	H	D	CH ₃	CD ₃
	705	H	H	D	CD ₃	CH ₃
	706	H	H	D	CD ₃	CD ₃
	707	H	D	H	CH ₃	CH ₃
	708	H	D	H	CH ₃	CD ₃
	709	H	D	H	CD ₃	CH ₃
60	710	H	D	H	CD ₃	CD ₃
	711	H	D	D	CH ₃	CH ₃
	712	H	D	D	CH ₃	CD ₃
	713	H	D	D	CD ₃	CH ₃
	714	H	D	D	CD ₃	CD ₃
	715	D	H	H	CH ₃	CH ₃
65	716	D	H	H	CH ₃	CD ₃
	111	D	H	H	CD ₃	CH ₃

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TABLE 7-continued

Cmpd	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	R ²	R ³
718	D	H	H	CD ₃	CD ₃
719	D	H	D	CH ₃	CH ₃
720	D	H	D	CH ₃	CD ₃
721	D	H	D	CD ₃	CH ₃
722	D	H	D	CD ₃	CD ₃
723	D	D	H	CH ₃	CH ₃
724	D	D	H	CH ₃	CD ₃
725	D	D	H	CD ₃	CH ₃
726	D	D	H	CD ₃	CD ₃
121	D	D	D	CH ₃	CH ₃
728	D	D	D	CH ₃	CD ₃
729	D	D	D	CD ₃	CH ₃
730	D	D	D	CD ₃	CD ₃
731	H	H	H	CH ₃	CH ₃

or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of Formula B-II, the compound is a compound selected from the group consisting of the compounds of Table 8, wherein X⁶ is hydrogen.

TABLE 8

Cmpd	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	R ²	R ³
800	H	H	H	CH ₃	CD ₃
801	H	H	H	CD ₃	CH ₃
802	H	H	H	CD ₃	CD ₃
803	H	H	D	CH ₃	CH ₃
804	H	H	D	CH ₃	CD ₃
805	H	H	D	CD ₃	CH ₃
806	H	H	D	CD ₃	CD ₃
807	H	D	H	CH ₃	CH ₃
808	H	D	H	CH ₃	CD ₃
809	H	D	H	CD ₃	CH ₃
810	H	D	H	CD ₃	CD ₃
811	H	D	D	CH ₃	CH ₃
812	H	D	D	CH ₃	CD ₃
813	H	D	D	CD ₃	CH ₃
814	H	D	D	CD ₃	CD ₃
815	D	H	H	CH ₃	CH ₃
816	D	H	H	CH ₃	CD ₃
817	D	H	H	CD ₃	CH ₃
818	D	H	H	CD ₃	CD ₃
819	D	H	D	CH ₃	CH ₃
820	D	H	D	CH ₃	CD ₃
821	D	H	D	CD ₃	CH ₃
822	D	H	D	CD ₃	CD ₃
823	D	D	H	CH ₃	CH ₃
824	D	D	H	CH ₃	CD ₃
825	D	D	H	CD ₃	CH ₃
826	D	D	H	CD ₃	CD ₃
827	D	D	D	CH ₃	CH ₃
828	D	D	D	CH ₃	CD ₃
829	D	D	D	CD ₃	CH ₃
830	D	D	D	CD ₃	CD ₃
831	H	H	H	CH ₃	CH ₃

or a pharmaceutically acceptable salt thereof.

In one embodiment of the compound of Formula B, the compound is a compound selected from the group consisting of the compounds of Table 9, wherein X^{1a} is deuterium and X^{1b} is hydrogen and each compound is a racemic mixture, and X⁶ is hydrogen:

TABLE 9

Cmpd	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	R ²	R ³
900	H	H	H	CH ₃	CD ₃
901	H	H	H	CD ₃	CH ₃

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TABLE 9-continued

Cmpd	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	R ²	R ³
902	H	H	H	CD ₃	CD ₃
903	H	H	D	CH ₃	CH ₃
904	H	H	D	CH ₃	CD ₃
905	H	H	D	CD ₃	CH ₃
906	H	H	D	CD ₃	CD ₃
907	H	D	H	CH ₃	CH ₃
908	H	D	H	CH ₃	CD ₃
909	H	D	H	CD ₃	CH ₃
910	H	D	H	CD ₃	CD ₃
911	H	D	D	CH ₃	CH ₃
912	H	D	D	CH ₃	CD ₃
913	H	D	D	CD ₃	CH ₃
914	H	D	D	CD ₃	CD ₃
915	D	H	H	CH ₃	CH ₃
916	D	H	H	CH ₃	CD ₃
917	D	H	H	CD ₃	CH ₃
918	D	H	H	CD ₃	CD ₃
919	D	H	D	CH ₃	CH ₃
920	D	H	D	CH ₃	CD ₃
921	D	H	D	CD ₃	CH ₃
922	D	H	D	CD ₃	CD ₃
923	D	D	H	CH ₃	CH ₃
924	D	D	H	CH ₃	CD ₃
925	D	D	H	CD ₃	CH ₃
926	D	D	H	CD ₃	CD ₃
927	D	D	D	CH ₃	CH ₃
928	D	D	D	CH ₃	CD ₃
929	D	D	D	CD ₃	CH ₃
930	D	D	D	CD ₃	CD ₃
931	H	H	H	CH ₃	CH ₃

or a pharmaceutically acceptable salt thereof.

In any one of the foregoing embodiments, examples, or aspects, any atom not designated as deuterium is present at its natural isotopic abundance.

In one embodiment of the compound of Formula E, the compound is a compound selected from the group consisting of the compounds of Table 10, wherein W is S(O)₂:

TABLE 10

Cmpd	X ^{2a} = X ^{2b}	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	X ⁶	R ¹	R ²	R ³
150	D	D	D	D	H	CD ₃	CD ₃	CD ₃
151	D	D	D	D	H	CD ₃	CH ₃	CH ₃
152	D	H	H	H	H	CD ₃	CH ₃	CH ₃
153	D	H	H	H	H	CD ₃	CD ₃	CD ₃
154	H	H	H	H	H	CH ₃	CD ₃	CD ₃
155	H	H	H	H	H	CH ₃	CH ₃	CH ₃
156	D	D	D	D	H	CD ₃	CD ₃	CH ₃
157	D	D	D	D	H	CD ₃	CH ₃	CD ₃
158	D	H	H	H	H	CD ₃	CH ₃	CD ₃
159	D	H	H	H	H	CD ₃	CD ₃	CH ₃
160	H	H	H	H	H	CH ₃	CD ₃	CH ₃
161	H	H	H	H	H	CH ₃	CH ₃	CD ₃

or a pharmaceutically acceptable salt thereof.

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 patent publication DE 860217; 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 237719, CS201558; PCT patent publication WO9531450; and in Japanese Patent publication Nos. JP58150594, JP58134092, JP58038284, JP57200391, JP57098284, JP57085387, JP57062278, JP57080385, JP57056481, JP57024385, JP57011981,

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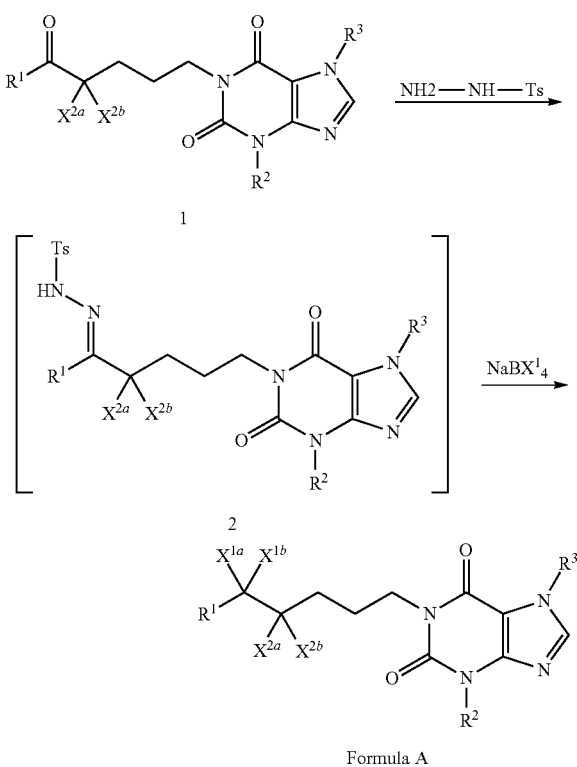
JP57024386, JP57024382, JP56077279, JP56032477, JP56007785, JP56010188, JP56010187, JP55122779, and JP55076876.

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.

Exemplary Synthesis

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

Scheme 1. Preparation of compounds of Formula A wherein each X¹ is the same, each X² is the same, each X³ is hydrogen, each X⁴ is hydrogen, each X⁵ is hydrogen' and X⁶ is hydrogen.



Cmpd	X ^{1a,b}	X ^{2a,b}	X ^{3a,b}	X ^{4a,b}	X ^{5a,b}	X ⁶	R ¹	R ²	R ³
102	D	D	H	H	H	H	CD ₃	CH ₃	CH ₃
103	D	D	H	H	H	H	CD ₃	CD ₃	CD ₃
104	H	D	H	H	H	H	CD ₃	CH ₃	CH ₃
105	H	D	H	H	H	H	CD ₃	CD ₃	CD ₃
106	D	H	H	H	H	H	CH ₃	CD ₃	CD ₃
107	D	H	H	H	H	H	CH ₃	CH ₃	CH ₃
110	D	D	H	H	H	H	CD ₃	CH ₃	CD ₃
111	D	D	H	H	H	H	CD ₃	CD ₃	CH ₃
112	H	D	H	H	H	H	CD ₃	CH ₃	CD ₃
113	H	D	H	H	H	H	CD ₃	CD ₃	CH ₃
114	D	H	H	H	H	H	CH ₃	CD ₃	CH ₃
115	D	H	H	H	H	H	CH ₃	CH ₃	CD ₃

An exemplary compound of Formula A may be prepared as shown in Scheme 1 by reduction with a source of X¹ (hydrogen or deuterium) of the corresponding ketone.

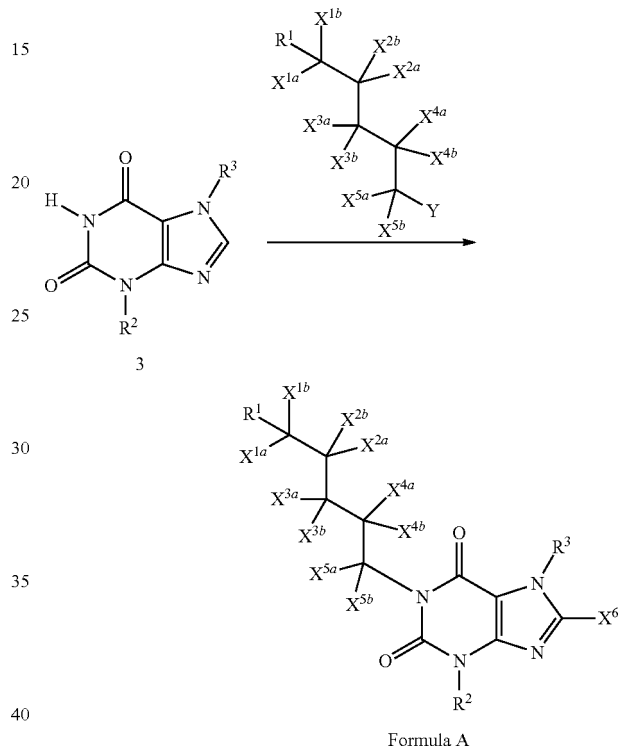
The ketone 1 is dissolved in a suitable solvent followed by addition of a hydrazide such as p-toluenesulfonyl hydrazide.

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The mixture is stirred for an amount of time sufficient to form the corresponding toluenesulfonyl hydrazone 2, after which time the source of X¹ is added to provide the compound of Formula A. A suitable source of X¹ is sodium borodeuteride (for X^{1a}=Z^{1b}=deuterium) or sodium borohydride (for X^{1a}=X^{1b}=hydrogen).

The ketones may be prepared, for example, as disclosed in Schemes 1a-12b of published patent application US 2009-0239886, which are incorporated by reference herein.

Scheme 2. Preparation of compounds of Formula A.

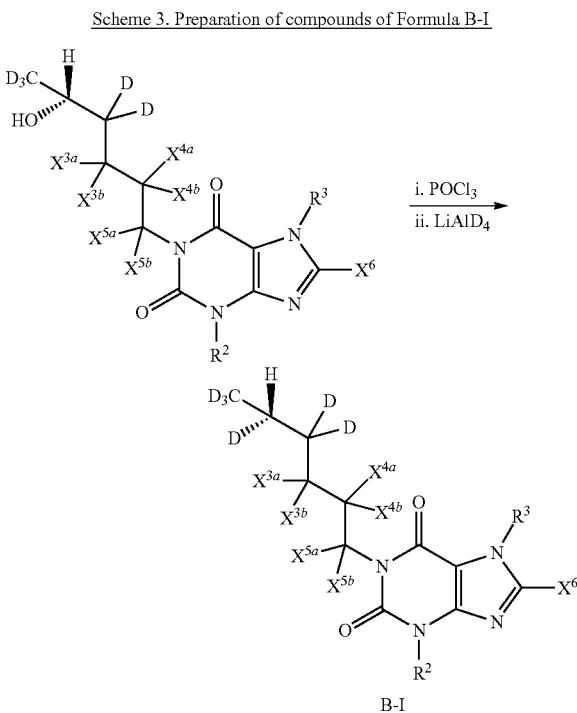


Compounds of Formula A may be prepared as shown in Scheme 2 above. As an example, the preparation is suitable for embodiments wherein each X¹ is deuterium, each X² is deuterium, each X³ is deuterium, each X⁴ is deuterium, each X⁵ is deuterium' and X⁶ is hydrogen. Alkylation of xanthine 3, deuterated as appropriate, to provide a compound of formula A as shown in Scheme 2A may be performed, as an example, in a manner analogous to the one disclosed in Scheme 1A published patent application corresponding to U.S. Ser. No. 12/380,579. Scheme 1A is incorporated by reference herein. As another example, the alkylation may be performed in a manner analogous to the procedure of Auclair (*J. Am. Chem. Soc.*, 2011, 113, 7853-7858) by treating with sodium hydride, followed by reaction with the alkylating agent, such as an alkyl bromide.

Appropriately deuterated xanthines may be prepared, for example, as disclosed in Schemes 13 and 14 of published patent application corresponding to U.S. Ser. No. 12/380,579. The schemes are incorporated by reference herein.

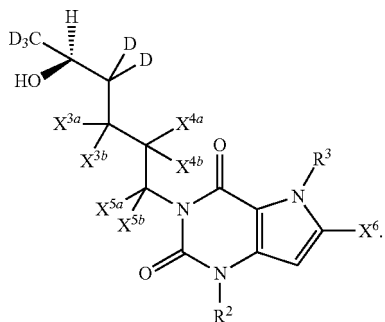
Compounds of Formula A wherein X^{1a} is deuterium and X^{1b} is hydrogen may be prepared by replacing with deuterium the hydroxyl group of the corresponding alcohols. As an example, the method disclosed in Althouse et al., *J. Am. Chem. Soc.* 1966, 88, p. 3595-90 may be used. The method is

suitable, for example, for the preparation of compounds of Formula B, such as the chiral compounds of Formula B-I, as disclosed in Scheme 3:



As shown in Scheme 3, a compound of Formula B-I may be prepared in a manner analogous to the one disclosed in Alt-house et al. from the alcohol having the formula shown in Scheme 3. The alcohol may be prepared, for example, as disclosed in Scheme 1B of the published patent application US20110077255. Scheme 1B is incorporated by reference herein in its entirety.

A compound of Formula B-II may be prepared in a similar manner to that disclosed in Scheme 3 from the alcohol having the formula



The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (i.e., R¹, R², R³, etc.) or not. The suitability of a chemi-

cal group in a compound structure for use in the synthesis of another compound is within the knowledge of one of ordinary skill in the art.

Additional methods of synthesizing compounds of this invention and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in Larock R, *Comprehensive Organic Transformations*, VCH Publishers (1989); Greene T W et al., *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); Fieser L et al., *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and Paquette L, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

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, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-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 LUTROLTM and PLURONICTM (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-butandiol. 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 can 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 Zafaroni, 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 petroleum, white petroleum, propylene glycol, polyoxyethylene 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-octyldodecanol, 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, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may option-

ally 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. Implantable 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, 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 pentifylline. Such agents include those indicated as being useful in combination with pentifylline, including but not limited to, those described in WO 1997019686, EP 0640342, WO 2003013568, WO 2001032156, WO 2006035418, and WO 1996005838.

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; 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, atheromatous 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, dipeptidyl-peptidase (DPP) IV inhibitors, other phosphodiesterase (PDE1, PDE5, PDE9, PDE10 or PDE1) inhibitors, amylin agonists, CoEnzyme A inhibitors, and antiobesity agents.

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, an 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 pentifylline.

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, including Formulae B, B-I and B-II.

In addition to its PDE inhibitory activity, pentifylline 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.

According to another embodiment, the invention provides a method of treating a disease in a patient in need thereof that is beneficially treated by pentifylline comprising the step of administering to said patient an effective amount of a compound of Formula A or a pharmaceutical composition comprising a compound of Formula A 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 1998055110, WO 2005023193, U.S. Pat. No. 4,975,432, WO 1993018770, EP 0490181, and WO 1996005836. Such diseases include, but are not limited to, 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; 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 syn-

drome; interleukin-1 mediated disease; graft versus host reaction and other allograft reactions; diet-induced fatty liver conditions, atheromatous 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; acute alcoholic hepatitis; olfaction disorders; patent ductus arteriosus; and inflammation or injury associated with neutrophil chemotaxis and/or degranulation.

The compounds of Formula A 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 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 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 *Pseudomonas* 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 pentifylline. 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 and a second therapeutic agent for treatment of the following conditions (with the particular second therapeutic agent indicated in parentheses following the indication): late radiation induced injuries (α -tocopherol), radiation-induced fibrosis (α -tocopherol), radiation induced lymphedema (α -tocopherol), chronic breast pain in breast cancer patients (α -tocopherol), type 2 diabetic nephropathy (captopril), malnutrition-inflammation-cachexia syndrome (oral nutritional supplement, such as Nepro; and oral anti-inflammatory module, such as Oxepa); and brain and central nervous system tumors (radiation therapy and hydroxyurea).

The combination therapies of this invention also include co-administering a compound of Formula A 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 an 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 meth-

ods. 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 Pharmacopoeia*, 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 would be 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 would be 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 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 for use in the treatment or prevention in a patient of a disease, disorder or symptom thereof delineated herein.

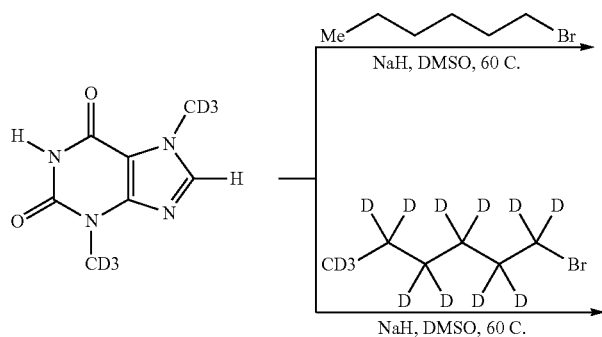
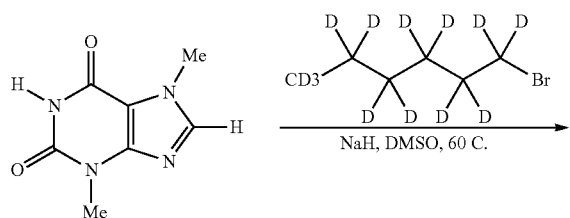
EXAMPLES

Example 1

General Procedure for Direct Alkylation of Xanthines

Deuterium-containing analogs of pentifylline were prepared in a manner analogous to the procedure of Auclair (*J. Am. Chem. Soc.*, 2011, 113, 7853-7858). A suspension of sodium hydride (1 equivalent) in dimethylsulfoxide (0.3M) was heated to 60 C. Once the solid had dissolved, the xanthine (1 equivalent), deuterated as appropriate, was added as a single portion and heated for 20 minutes. The appropriate alkyl bromide (1 equivalent) was then added as a single portion via syringe. The reaction was heated for 12 h additional upon which it was deemed complete by LCMS. The reaction was cooled, diluted with chloroform and washed with a saturated aqueous solution of ammonium chloride. The combined organic phases were dried over sodium sulfate, filtered and concentrated. The desired product was purified by silica gel chromatography on a Teledyne ISCO Combiflash system with a gradient methanol-dichloromethane solvent system (0-10%). Using the above procedure and starting with undeuterated or appropriately deuterated xanthines (which may be prepared, for example, as disclosed in Schemes 13 and 14 of U.S. Ser. No. 12/380,579), compounds 100, 101 and 116 were prepared as shown schematically below:

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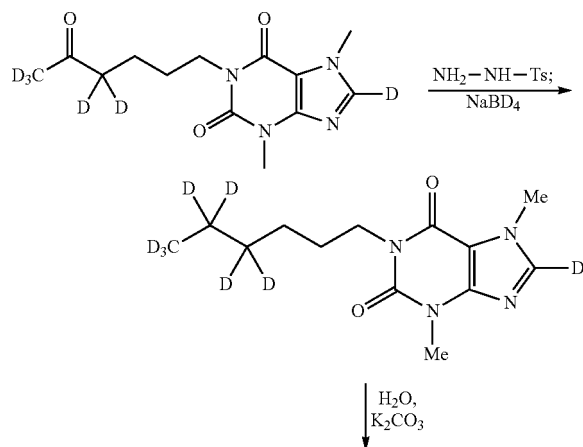
3,7-dimethyl-1-(perdeuteriohexyl)-1H-purine-2,6(3H,7H)-dione 100: The desired product was obtained as a white powder (236 mg, 0.851 mmol, 85% yield)¹H NMR (400 MHz, CDCl₃) δ: 7.51 (s, 1H), 3.97 (s, 3H), 3.46 (s, 3H). MS(ESI+) 278.3 [(M+H)⁺].

1-(perdeuteriohexyl)-3,7-bis(trideuteriomethyl)-1H-purine-2,6(3H,7H)-dione 101: The desired product was obtained as a white powder (22 mg, 0.078 mmol, 8% yield)¹H NMR (400 MHz, CDCl₃) δ: 7.51 (s, 1H) MS(ESI+) 284.4 [(M+H)⁺].

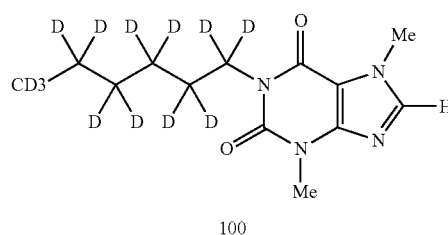
1-hexyl-3,7-bis(trideuteriomethyl)-1H-purine-2,6(3H,7H)-dione 116: The desired product was obtained as a white powder (22 mg, 0.16 mmol, 16% yield)¹H NMR (400 MHz, CDCl₃) δ: 7.51 (s, 1H), 4.03 (t, J=7.7 Hz, 2H), 1.64 (m, 2H), 1.37 (m, 6H), 1.26 (m, 3H). MS(ESI+) 271.1 [(M+H)⁺].

Example 2

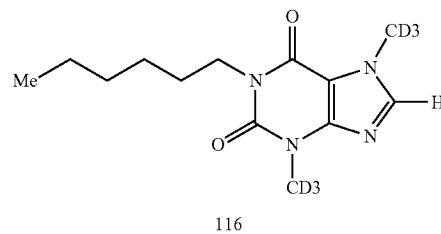
Preparation of Compound 102



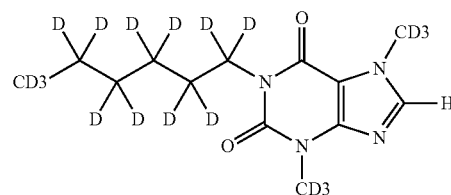
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100



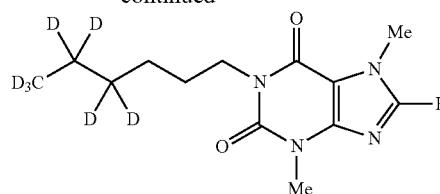
116



101

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-continued



102

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3,7-dimethyl-1-(4,4,6,6,6-pentadeutero-5-oxohexyl)-1H-purine-2,6(3H,7H)-dione (0.5 g, 1.76 mmol) which may be prepared, for example, as disclosed in published patent application corresponding to U.S. Ser. No. 12/380,579, was condensed with tosyl hydrazine (0.328 g, 1.76 mmol.) was performed in methanol-D1 (3.3 mL) at ambient temperature for four hours. Sodium borodeuteride (221 mg, 5.28 mmol) was then added slowly to avoid exotherm. The reaction was heated to a gentle reflux for 48 hours. After cooling to ambient temperature, the reaction was diluted with dichloromethane and washed with aqueous hydrochloric acid solution (1M). The combined organics were dried over sodium sulfate, filtered and concentrated to dryness. The desired product was purified by silica gel chromatography on a Teledyne ISCO Combiflash system with a gradient methanol-dichloromethane solvent system (0-10%). Deuterium-to-hydrogen exchange was performed as disclosed in published patent application corresponding to U.S. Ser. No. 12/380,579, to provide compound 102, 1-(4,4,5,5,6,6,6-heptadeuteriohexyl)-3,7-dimethyl-1H-purine-2,6(3H,7H)-dione. The desired product was obtained as a white powder (28 mg, 0.103 mmol, 10% yield)¹H NMR (400 MHz, CDCl₃) δ: 7.51 (s, 1H), 3.97 (s, 3H), 3.94 (m, 2H), 3.46 (s, 3H) 1.64 (m, 2H), 1.37 (m, 2H). MS (ESI+) 272.3 [(M+H)⁺].

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Biological Evaluation

The metabolic stability of the compounds of the invention may be evaluated according to one or both of the following methods:

Example 1

Evaluation of Compound Stability in Human Liver Microsomes. Comparison of Compounds and Pentifylline

Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, Kans.). β -nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride ($MgCl_2$), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

Determination of Metabolic Stability:

7.5 mM stock solutions of test compounds are prepared in DMSO. The 7.5 mM stock solutions are diluted to 12.5-50 μ M in acetonitrile (ACN). The 20 mg/mL human liver microsomes are diluted to 0.625 mg/mL in 0.1 M potassium phosphate buffer, pH 7.4, containing 3 mM $MgCl_2$. The diluted microsomes are added to wells of a 96-well deep-well polypropylene plate in triplicate. A 10 μ L aliquot of the 12.5-50 μ M test compound is added to the microsomes and the mixture is pre-warmed for 10 minutes. Reactions are initiated by addition of pre-warmed NADPH solution. The final reaction volume is 0.5 mL and contains 0.5 mg/mL human liver microsomes, 0.25-1.0 μ M test compound, and 2 mM NADPH in 0.1 M potassium phosphate buffer, pH 7.4, and 3 mM $MgCl_2$. The reaction mixtures are incubated at 37° C., and 50 μ L aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μ L of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4° C. for 20 minutes after which 100 μ L of water is added to the wells of the plate before centrifugation to pellet precipitated proteins. Supernatants are transferred to another 96-well plate and analyzed for amounts of parent remaining by LC-MS/MS using an Applied Bio-systems API 4000 mass spectrometer. The same procedure is followed for the non-deuterated counterpart of the compound of Formula I and the positive control, 7-ethoxycoumarin (1 μ M). Testing is done in triplicate.

Data Analysis:

The in vitro $t_{1/2}$ s for test compounds are calculated from the slopes of the linear regression of % parent remaining (ln) vs incubation time relationship.

$$\text{in vitro } t_{1/2} = 0.693/k$$

$k = -[\text{slope of linear regression of \% parent remaining}(\ln) \text{ vs incubation time}]$ Data analysis is performed using Microsoft Excel Software.

Example 2

In Vivo Assay

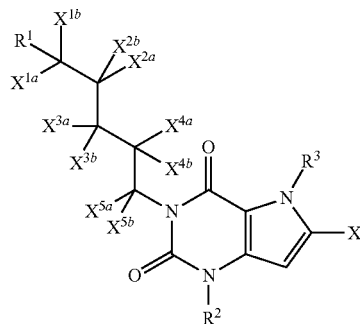
Male, Sprague-Dawley rats are administered a 10-100 mg/kg dose of the test compound intravenously via a cannula or PO via oral gavage with. Blood samples are collected pre-dose and at approximately 8 time points up to 24 hours post-dose. Plasma samples are obtained from the blood and analyzed for concentrations of the dosed test article by LC-MS/MS.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the illustrative examples, make and utilize the compounds of 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 A:

Formula A



or pharmaceutically acceptable salts thereof, wherein each of X^{1a}, X^{1b}, X^{2a}, and X^{2b} is deuterium; each of X^{3a}, X^{3b}, X^{4a}, X^{4b}, X^{5a}, X^{5b} and X⁶ is hydrogen; R¹ is —CD₃; and each of R² and R³ is independently CH₃ or CD₃.

2. The compound of claim 1, wherein R³ and R² are each —CD₃.

3. The compound of claim 1, wherein R³ and R² are each —CH₃.

4. The compound of claim 1, wherein R³ is —CH₃ and R² is —CD₃.

5. The compound of claim 1, wherein R² is —CH₃ and R³ is —CD₃.

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

7. The compound of claim 1, wherein the compound is a compound selected from the group consisting of the compounds of Table 1 and wherein any atom not designated as deuterium is present at its natural isotopic abundance:

TABLE 1

Cmpd	X ^{1a} = X ^{1b}	X ^{2a} = X ^{2b}	X ^{3a} = X ^{3b}	X ^{4a} = X ^{4b}	X ^{5a} = X ^{5b}	X ⁶	R ¹	R ²	R ³
102	D	D	H	H	H	H	CD ₃	CH ₃	CH ₃
103	D	D	H	H	H	H	CD ₃	CD ₃	CD ₃
110	D	D	H	H	H	H	CD ₃	CH ₃	CD ₃
111	D	D	H	H	H	H	CD ₃	CD ₃	CH ₃

or a pharmaceutically acceptable salt thereof.

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

9. A method of therapeutic or prophylactic treatment of intermittent claudication in a patient in need thereof, comprising administering to the patient an effective amount of a compound of claim 1.

* * * * *