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61/296,264 19 January 2010 (19.01.2010) US(71) Applicant (for all designated States except US): **CON-
CERT PHARMACEUTICALS, INC.** [US/US]; 99
Hayden Avenue, Suite 500, Lexington, MA 02421 (US).

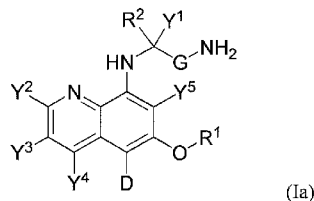
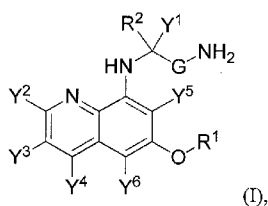
(72) Inventor; and

(75) Inventor/Applicant (for US only): **TUNG, Roger**
[US/US]; 99 Hayden Avenue, Lexington, MA 02421
(US).(74) Agents: **ABELLEIRA, Susan, M.** et al.; Hamilton,
Brook, Smith & Reynolds, P.C., 530 Virginia Rd, P.O.
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(54) Title: AMINOQUINOLINE DERIVATIVES



(57) Abstract: This invention relates to novel aminoquinoline derivatives of Formula (I) or Ia, or pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering an aminoquinoline derivative, such as a derivative of primaquine.

AMINOQUINOLINE DERIVATIVES

RELATED APPLICATION

[1] This application claims the benefit of U.S. Provisional Application No. 61/296,264 filed on January 19, 2010, the entire teachings of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[2] 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 often fail to address the underlying ADME problems that exist for many drugs and drug candidates. One such problem is 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.

[3] In some select cases, a metabolic inhibitor will be co-administered with a drug that is cleared too rapidly. Such is the case with the protease inhibitor class of drugs that are used to treat HIV infection. The FDA recommends that these drugs be co-dosed with ritonavir, an inhibitor of cytochrome P450 enzyme 3A4 (CYP3A4), the enzyme typically responsible for their metabolism (see Kempf, DJ. et al, Antimicrobial Agents and Chemotherapy, 1997, 41(3): 654-60). Ritonavir, however, causes adverse effects and adds to the pill burden for HIV patients who must already take a combination of different drugs. Similarly, the CYP2D6 inhibitor quinidine has been added to dextromethorphan for the purpose of reducing rapid CYP2D6

metabolism of dextromethorphan in a treatment of pseudobulbar affect. Quinidine, however, has unwanted side effects that greatly limit its use in potential combination therapy (see Wang, L et al, Clin Pharmacol Therap, 1994, 56(6 Pt 1): 659-67; and FDA label for quinidine at www.accessdata.fda.gov).

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

[5] A potentially attractive strategy 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. Compared to hydrogen, deuterium forms stronger bonds with carbon. 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/or tolerability. At the same time, because the size and shape of deuterium are essentially identical to those of 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.

[6] 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, MI et al, J Pharm Sci, 1975, 64:367-91; Foster, AB, Adv Drug Res 1985, 14:1-40 ("Foster"); Kushner, DJ et al, Can J Physiol Pharmacol 1999, 79-88; Fisher, MB 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 increased 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).

[7] 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 non-deuterated counterpart. See, for example, Fukuto et al, J Med Chem 1991, 34, 2871-76). 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

[8] This invention relates to novel deuterium-substituted aminoquinoline derivatives, or pharmaceutically acceptable salts thereof. This invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering a deuterium-substituted aminoquinoline derivative, such as, deuterium- substituted primaquine.

[9] Primaquine, also known as *N*-(6-methoxyquinolin-8-yl)pentane-1,4-diamine phosphate is an anti-malarial that has been used since 1950. It is typically used for radical cure of malaria -- a 14 day course of treatment that removes the latent or dormant form of the parasite (hypnozoite) from the liver of infected individuals following clearance of the parasite from the bloodstream. It is typically administered in conjunction with quinine or chloroquine.

[10] The use of primaquine, however is dose-limiting because of side effects. It causes methemoglobinemia in all patients and can cause hemolytic anemia in people of African or Mediterranean descent and in anyone with a glucose-6-phosphate dehydrogenase deficiency. It is contraindicated in pregnant females because the G-6-PD status of the fetus is unknown. It has been suggested that certain cytochrome P450-generated metabolites of primaquine are responsible for its hemotoxicity (Ganesan, S et al, Toxicol Appl Pharmacol 2009, doi:10.1026/j.taap.2009.07.012)

[11] Despite the beneficial activities of primaquine, there is a continuing need for new compounds to treat the aforementioned diseases and conditions, which may avoid some of the undesired side effects and which may be useful in individuals for whom primaquine is contraindicated.

DETAILED DESCRIPTION OF THE INVENTION

[12] The term “treat” means 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.

[13] “Disease” means any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

[14] 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 primaquine 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, LZ et al, Comp Biochem Physiol Mol Integr Physiol, 1998, 119:725.

[15] 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).

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

[17] 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).

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

[19] 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. In other embodiments, the relative amount of such isotopologues *in toto* will be less than 47.5%, less than 40%, less than 32.5%, less than 25%, less than 17.5%, less than 10%, less than 5%, less than 3%, less than 1%, or less than 0.5% of the compound.

[20] The invention also provides salts of the compounds of the invention.

[21] 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.

[22] Unless otherwise stated, throughout the application all references to “a compound of Formula I” or “a compound of Formula Ia” include, within the scope of each such term, pharmaceutically acceptable salts of such compound(s).

[23] 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.

[24] Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, 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.

[25] The compounds of the present invention (e.g., compounds of Formula I), may contain an asymmetric carbon atom, for example, as the result of deuterium substitution or otherwise. As such, compounds of this invention can exist as either individual enantiomers, or mixtures of the two enantiomers. Accordingly, a compound of the present invention may exist as either a racemic mixture or a scalemic mixture, or 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 are present. Methods of obtaining or synthesizing an individual enantiomer for a given compound are known in the art and may be applied as practicable to final compounds or to

starting material or intermediates.

[26] 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.

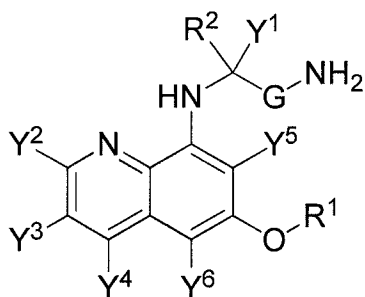
[27] The term “stable compounds,” as used herein, refers to compounds which possess stability sufficient to allow for their manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products,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

[28] “D” and “d” both refer to deuterium. “Stereoisomer” refers to both enantiomers and diastereomers. “Tert” and “t-” each refer to tertiary. “US” refers to the United States of America.

[29] Throughout this specification, a variable may be referred to generally (e.g., “each R”) or may be referred to specifically (e.g., R^1 , R^2 , R^3 , etc.). Unless otherwise indicated, when a variable is referred to generally, it is meant to include all specific embodiments of that particular variable.

THERAPEUTIC COMPOUNDS

[30] The present invention provides a compound of Formula I:



(I), wherein:

each of R^1 and R^2 is independently selected from $-CH_3$, $-CH_2D$, $-CHD_2$ and $-CD_3$;

each Y is independently selected from hydrogen and deuterium; and

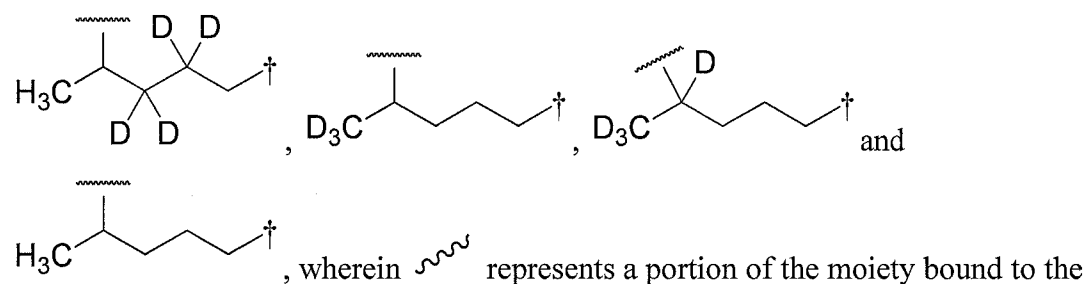
G is n-propylene optionally substituted with 1-6 deuterium,

provided that if G is $-CH_2CH_2CD_2-$, $R^1 = R^2 = CH_3$ and $Y^1 = H$, or if G is $-(CH_2)_3-$, $R^1 = R^2 = CH_3$ and $Y^1 = D$, then at least one of Y^2 , Y^3 , Y^4 , Y^5 and Y^6 is D,

further provided that if G is $-(CH_2)_3-$, $R^1 = R^2 = CH_3$ and $Y^1 = H$, then at least two of Y^2, Y^3, Y^4, Y^5 and Y^6 is D wherein “†” represents a portion of G bound to the terminal $-NH_2$ group.

[31] In one embodiment of the compound of Formula I, G is selected from $-(CD_2)_3-$, $-(CH_2)_3-$, $-CH_2CH_2CD_2-\dagger$ and $-CH_2CD_2CD_2-\dagger$, wherein “ $\dagger$ ” represents a portion of G bound to the terminal $-NH_2$ group in the compound and each of R^1 and R^2 is independently selected from $-CD_3$ and $-CH_3$. In one aspect of this embodiment, the

moiety -C(R²)(Y¹)-G-† is selected from



internal -NH- group. In still another aspect of this embodiment, each of Y², Y³, Y⁴, Y⁵ and Y⁶ are the same.

[32] In one embodiment of the compound of Formula I, Y⁵ and Y⁶ are hydrogen. In one aspect of this embodiment, G is selected from -(CD₂)₃-, -(CH₂)₃-, -CH₂CH₂CD₂-† and -CH₂CD₂CD₂-†. In another aspect of this embodiment, each of R¹ and R² is selected from -CD₃ and -CH₃. In a more specific aspect of this embodiment, G is selected from -(CD₂)₃-, -(CH₂)₃-, -CH₂CH₂CD₂-† and -CH₂CD₂CD₂-†; and each of R¹ and R² is selected from -CD₃ and -CH₃.

[33] In one embodiment of the compound of Formula I, Y², Y³, Y⁴, Y⁵ and Y⁶ are the same (i.e. all simultaneously deuterium or all simultaneously hydrogen). In one aspect of this embodiment, G is selected from -(CD₂)₃-, -(CH₂)₃-, -CH₂CH₂CD₂-† and -CH₂CD₂CD₂-†. In another aspect of this embodiment, each of R¹ and R² is selected from -CD₃ and -CH₃. In a more specific aspect of this embodiment, G is selected from -(CD₂)₃-, -(CH₂)₃-, -CH₂CH₂CD₂-† and -CH₂CD₂CD₂-†; and each of R¹ and R² is selected from -CD₃ and -CH₃.

[34] 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.

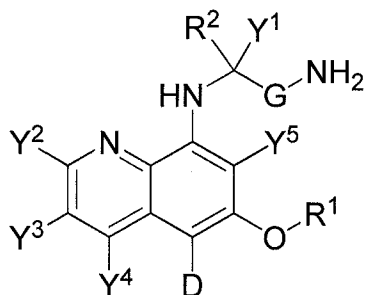
[35] In still another embodiment, the compound of Formula I is selected from any one of the compounds set forth in Table 1 or a pharmaceutically acceptable salt thereof.

Table 1. Exemplary Compounds of Formula I

Cmpd #	R ¹	R ²	Y ¹	G	Each of Y ² , Y ³ , Y ⁴	Each of Y ⁵ , Y ⁶
200	-CH ₃	-CD ₃	D	-(CD ₂) ₃ -†	H	H
201	-CH ₃	-CD ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	H
202	-CH ₃	-CD ₃	D	-CH ₂ CD ₂ CD ₂ -†	H	H
203	-CH ₃	-CD ₃	D	-(CH ₂) ₃ -†	H	H
204	-CH ₃	-CD ₃	H	-(CD ₂) ₃ -†	H	H
205	-CH ₃	-CD ₃	H	-CH ₂ CH ₂ CD ₂ -†	H	H
206	-CH ₃	-CD ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	H
207	-CH ₃	-CD ₃	H	-(CH ₂) ₃ -†	H	H
208	-CD ₃	-CD ₃	D	-(CD ₂) ₃ -†	H	H
209	-CD ₃	-CD ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	H
210	-CD ₃	-CD ₃	D	-CH ₂ CD ₂ CD ₂ -†	H	H
211	-CD ₃	-CD ₃	D	-(CH ₂) ₃ -†	H	H
212	-CD ₃	-CD ₃	H	-(CD ₂) ₃ -†	H	H
213	-CD ₃	-CD ₃	H	-CH ₂ CH ₂ CD ₂ -†	H	H
214	-CD ₃	-CD ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	H
215	-CD ₃	-CD ₃	H	-(CH ₂) ₃ -†	H	H
216	-CH ₃	-CH ₃	D	-(CD ₂) ₃ -†	H	H
217	-CH ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	H
218	-CH ₃	-CH ₃	D	-CH ₂ CD ₂ CD ₂ -†	H	H
219	-CD ₃	-CH ₃	D	-(CD ₂) ₃ -†	H	H
220	-CD ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	H
221	-CD ₃	-CH ₃	D	-CH ₂ CD ₂ CD ₂ -†	H	H
222	-CD ₃	-CH ₃	D	-(CH ₂) ₃ -†	H	H
223	-CD ₃	-CH ₃	H	-(CD ₂) ₃ -†	H	H
224	-CD ₃	-CH ₃	H	-CH ₂ CH ₂ CD ₂ -†	H	H
225	-CD ₃	-CH ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	H

Cmpd #	R ¹	R ²	Y ¹	G	Each of Y ² , Y ³ , Y ⁴	Each of Y ⁵ , Y ⁶
226	-CD ₃	-CH ₃	H	-(CH ₂) ₃ -†	H	H
227	-CH ₃	-CH ₃	H	-(CD ₂) ₃ -†	H	H
228	-CH ₃	-CH ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	H

[36] The compound of Formula I in one embodiment is a compound of Formula Ia:



(Ia), wherein:

each of R¹ and R² is independently selected from -CH₃, -CH₂D, -CHD₂ and -CD₃;

each Y is independently selected from hydrogen and deuterium; and

G is n-propylene optionally substituted with 1-6 deuterium provided that at least one of R¹, R², G, Y¹, Y², Y³, Y⁴, and Y⁵ comprises D.

[37] In one embodiment of the compound of Formula Ia, G is selected from -(CD₂)₃-, -(CH₂)₃-, -CH₂CH₂CD₂-† and -CH₂CD₂CD₂-†, wherein “†” represents a portion of G bound to the terminal -NH₂ group in the compound and each of R¹ and R² is independently selected from -CD₃ and -CH₃. In one aspect of this embodiment,

the moiety -C(R²)(Y¹)-G-† is selected from

and H₃C-CH₂-CH₂-CH₂-†, wherein represents a portion of the moiety bound to the internal -NH- group. In still another aspect of this embodiment, each of Y², Y³, Y⁴ and Y⁵ are the same.

[38] In one embodiment of the compound of Formula Ia, Y^5 is deuterium. In one aspect of this embodiment, G is selected from $-(CD_2)_3-$, $-(CH_2)_3-$, $-CH_2CH_2CD_2-\dagger$ and $-CH_2CD_2CD_2-\dagger$. In another aspect of this embodiment, each of R^1 and R^2 is selected from $-CD_3$ and $-CH_3$. In a more specific aspect of this embodiment, G is selected from $-(CD_2)_3-$, $-(CH_2)_3-$, $-CH_2CH_2CD_2-\dagger$ and $-CH_2CD_2CD_2-\dagger$; and each of R^1 and R^2 is selected from $-CD_3$ and $-CH_3$.

[39] In one embodiment of the compound of Formula Ia, Y^2 , Y^3 , Y^4 , and Y^5 are the same (i.e. all simultaneously deuterium or all simultaneously hydrogen). In one aspect of this embodiment, G is selected from $-(CD_2)_3-$, $-(CH_2)_3-$, $-CH_2CH_2CD_2-\dagger$ and $-CH_2CD_2CD_2-\dagger$. In another aspect of this embodiment, each of R^1 and R^2 is selected from $-CD_3$ and $-CH_3$. In a more specific aspect of this embodiment, G is selected from $-(CD_2)_3-$, $-(CH_2)_3-$, $-CH_2CH_2CD_2-\dagger$ and $-CH_2CD_2CD_2-\dagger$; and each of R^1 and R^2 is selected from $-CD_3$ and $-CH_3$.

[40] 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.

[41] In still another embodiment, the compound of Formula Ia is selected from any one of the compounds set forth in Table 2 or a pharmaceutically acceptable salt thereof.

Table 2. Exemplary Compounds of Formula Ia

Cmpd #	R^1	R^2	Y^1	G	Each of Y^2, Y^3, Y^4	Y^5
100	$-CH_3$	$-CD_3$	D	$-(CD_2)_3-\dagger$	D	D
101	$-CH_3$	$-CH_3$	D	$-CH_2CH_2CD_2-\dagger$	D	D
102	$-CH_3$	$-CH_3$	H	$-CH_2CD_2CD_2-\dagger$	D	D
103	$-CH_3$	$-CD_3$	H	$-(CH_2)_3-\dagger$	D	D
104	$-CH_3$	$-CD_3$	D	$-(CH_2)_3-\dagger$	D	D
105	$-CH_3$	$-CH_3$	H	$-(CH_2)_3-\dagger$	D	D
106	$-CD_3$	$-CD_3$	D	$-(CD_2)_3-\dagger$	D	D
107	$-CD_3$	$-CH_3$	D	$-CH_2CH_2CD_2-\dagger$	D	D
108	$-CD_3$	$-CH_3$	H	$-CH_2CD_2CD_2-\dagger$	D	D
109	$-CD_3$	$-CD_3$	H	$-(CH_2)_3-\dagger$	D	D
110	$-CD_3$	$-CD_3$	D	$-(CH_2)_3-\dagger$	D	D
111	$-CD_3$	$-CH_3$	H	$-(CH_2)_3-\dagger$	D	D
112	$-CH_3$	$-CD_3$	D	$-(CD_2)_3-\dagger$	H	D

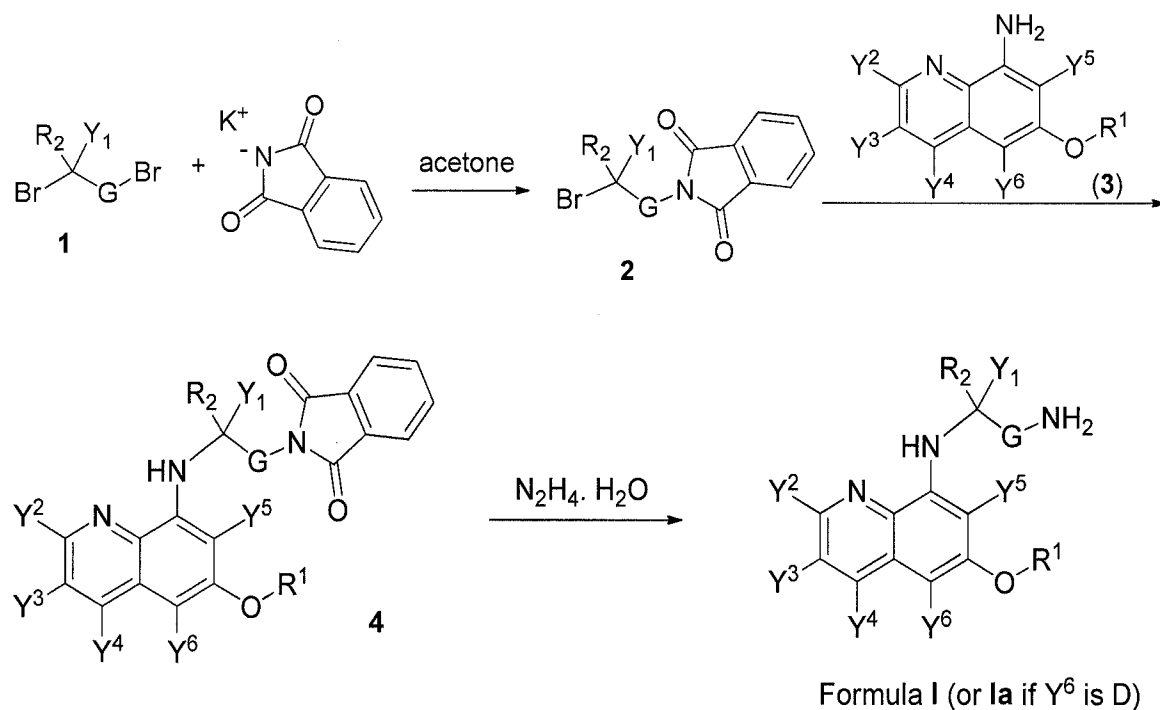
Cmpd #	R ¹	R ²	Y ¹	G	Each of Y ² , Y ³ , Y ⁴	Y ⁵
113	-CH ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	D
114	-CH ₃	-CH ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	D
115	-CH ₃	-CD ₃	H	-(CH ₂) ₃ -†	H	D
116	-CH ₃	-CD ₃	D	-(CH ₂) ₃ -†	H	D
117	-CH ₃	-CH ₃	H	-(CH ₂) ₃ -†	H	D
118	-CD ₃	-CD ₃	D	-(CD ₂) ₃ -†	H	D
119	-CD ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	D
120	-CD ₃	-CH ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	D
121	-CD ₃	-CD ₃	H	-(CH ₂) ₃ -†	H	D
122	-CD ₃	-CD ₃	D	-(CH ₂) ₃ -†	H	D
123	-CD ₃	-CH ₃	H	-(CH ₂) ₃ -†	H	D

[42] The synthesis of compounds of Formula I or Ia may be readily achieved by synthetic chemists of ordinary skill by reference to the Exemplary Synthesis and Examples disclosed herein. Relevant procedures analogous to those of use for the preparation of compounds of Formula I or Ia and intermediates thereof are disclosed, for instance in Elderfield, RC et al., J Am Chem Soc, 1955, 77(18): 4816.

[43] 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.

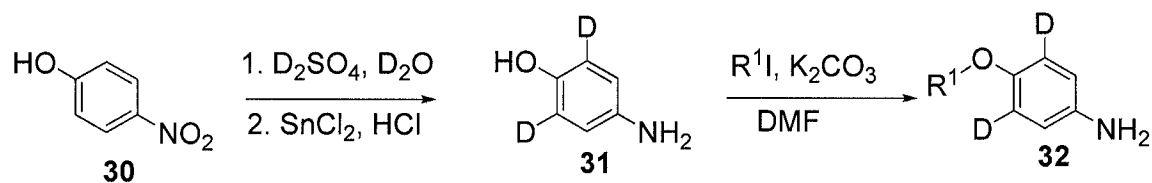
Exemplary Synthesis

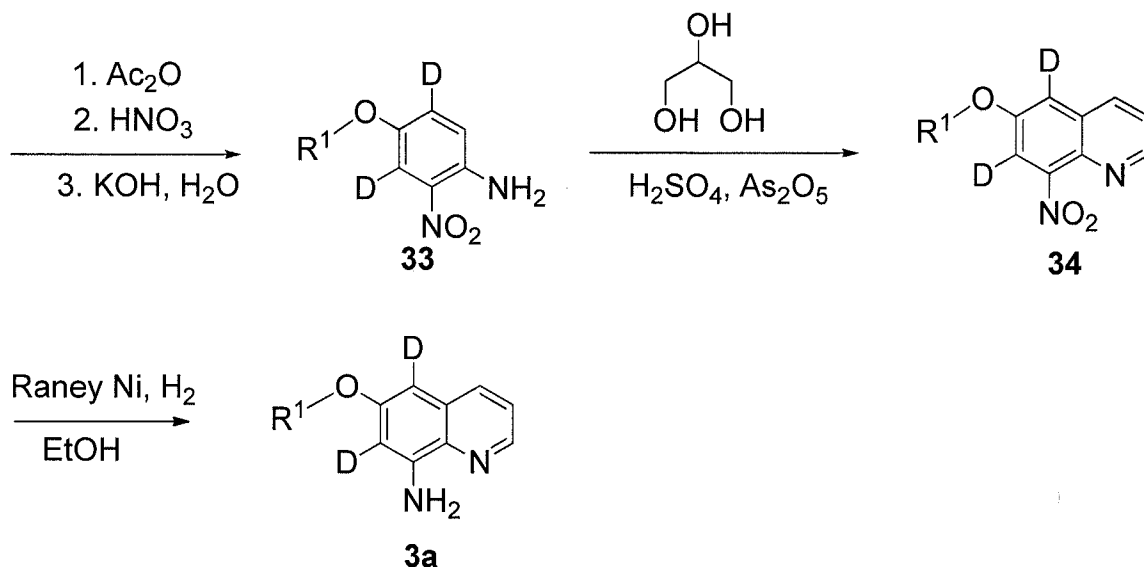
[44] A convenient method for synthesizing compounds of Formula I (or Ia if Y⁶ is D) is depicted in Scheme 1.

Scheme 1. A Method for Preparation of Compounds of Formula I (or Ia if Y⁶ is D).

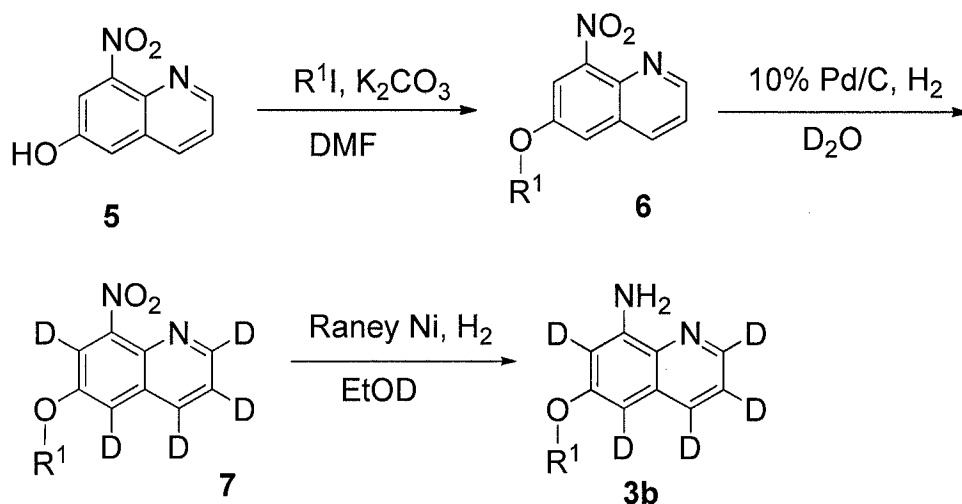
[45] Scheme 1 may be used to prepare compounds of Formula I (or Ia if Y⁶ is D). As shown in Scheme 1, an appropriately deuterated 1,4-dibromopentane **1** may be heated with potassium phthalimide to provide **2**. Heating of **2** with an appropriately deuterated aminoquinoline **3**, optionally in the presence of a base, gives **4**. Treatment of **4** with hydrazine provides a compound of Formula I (or Ia if Y⁶ is D).

[46] An appropriately deuterated aminoquinoline **3** may be prepared as shown in Scheme 2a or 2b below.

Scheme 2a. Preparation of Deuterated Aminoquinoline **3a**.

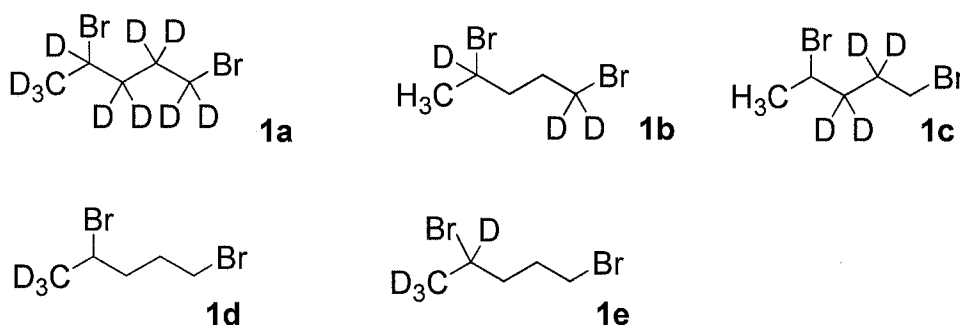


[47] A convenient method for synthesizing aminoquinoline **3a**, in which Y^5 and Y^6 are deuterium, is depicted in Scheme 2a. Treatment of the 4-nitrophenol (**30**) with deuterated sulfuric acid in deuterium oxide followed by reduction of the nitro group with tin (II) chloride according to the procedure described by Suehiro, T et al, Bull Chem Soc Japan, 1987, 33:3321-3330 affords the dideutero phenol **31**. Treatment of **31** with the appropriately deuterated alkyl iodide using a procedure analogous to that described by Schmid, J, et al, WO 2007/147115 A2 affords aniline **32**. Acetylation of **32** with acetic anhydride, followed by nitration of the corresponding acetamide with nitric acid then hydrolysis of the acetamide moiety with aqueous potassium hydroxide using a procedure analogous to that described by Tarbell, DS et al, Org Synth, 1945, 25: 78-79 gives nitroaniline **33**. Treatment of **33** with glycerol in the presence of sulfuric acid and arsenic oxide using a procedure analogous to that described by Mosher, HS. et al, Org Synth, 1947, 27: 48-49 results in cyclization to form nitroquinoline **34**. Reduction of the nitro group in **34** with H_2 and Raney Nickel using a procedure analogous to that described by Vangapandu, S, et al, Bioorg Med Chem, 2004, 12: 2501-2508 gives the aminoquinoline **3a**.

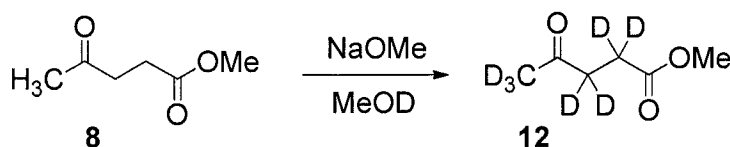
Scheme 2b. Preparation of Deuterated Aminoquinoline **3b**.

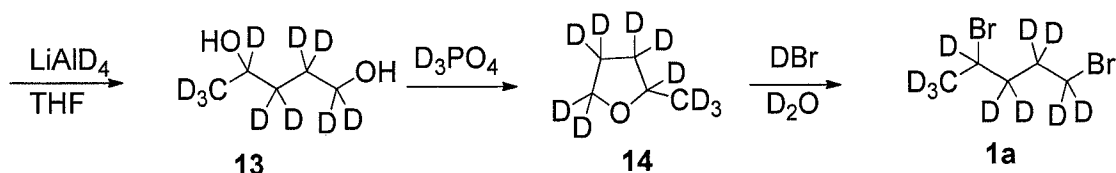
[48] A convenient method for synthesizing aminoquinoline **3b**, in which each of Y^2 , Y^3 , Y^4 , Y^5 and Y^6 is deuterium, is depicted in Scheme 2b. 6-hydroxy-8-nitroquinoline **5** is treated with an appropriately deuterated methyl iodide in a manner analogous to the one described in WO 2007/147115 to provide an appropriately deuterated methoxynitroquinoline **6**. **6** is converted to **7** by treatment with H_2 and 10% Pd/C in D_2O , analogously to what is described in Sajiki et al, Tetrahedron, 2006, 62:10954-61. Reduction of the nitro group of **6** with H_2 and Raney nickel followed by quenching with CH_3CH_2OD affords **3b**, in a manner analogous to what is described in Vangapandu, S, et al, Biorg Med Chem, 2004, 12: 2501-08.

[49] An appropriately deuterated 1,4-dibromopentane **1** for use in Scheme 1 may be, for example, any one of compounds **1a-1e**:



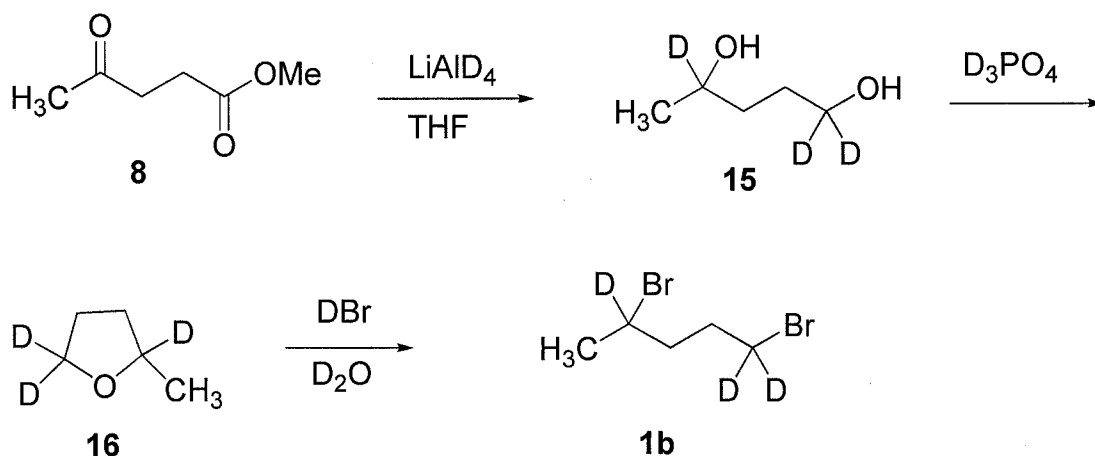
[50] The preparation of **1a-1e** is shown in Schemes 3a-e, respectively:

Scheme 3a. Preparation of 1,4-dibromo-d10-pentane **1a**.

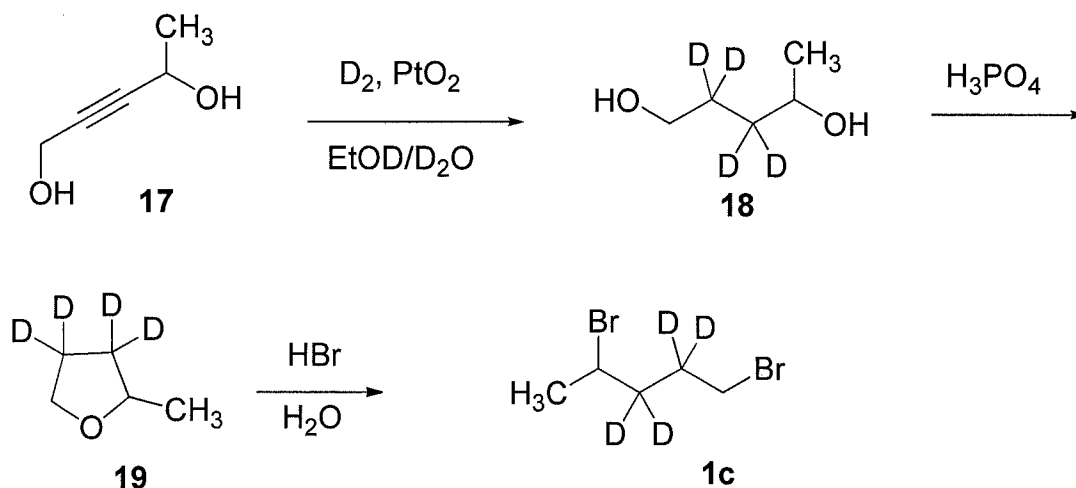


[51] As shown in Scheme 3a, methyl levulinate **8** is treated with sodium methoxide and CH_3OD to give **12**. Alternatively, **8** may be converted to **12** using (i) $\text{NaOD}/\text{D}_2\text{O}$, (ii) $\text{CH}_3\text{OD}/\text{D}_2\text{SO}_4$, (iii) $\text{NaOCH}_3/\text{CH}_3\text{OD}$ following the method described in Clement, J-L, et al.; Org. Biomol. Chem. 2003, 1, 1591-1597. Reduction of **12** with LiAlD_4 gives diol **13** which cyclizes to **14** upon treatment with D_3PO_4 . Ring-opening of **14** with DBr and D_2O in a manner analogous to the procedure of Leonard, NJ et al, J Am Chem Soc, 1952, 74: 917-20 provides **1a**.

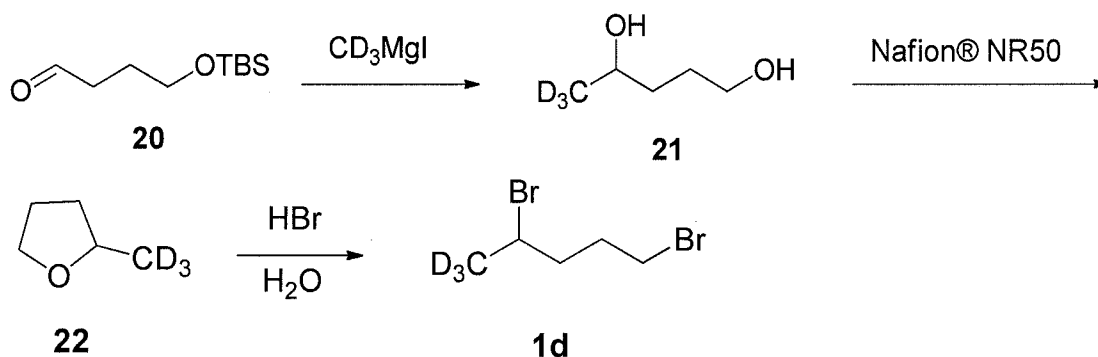
Scheme 3b. Preparation of 1,4-dibromo-1,1,4-d3-pentane **1b**.



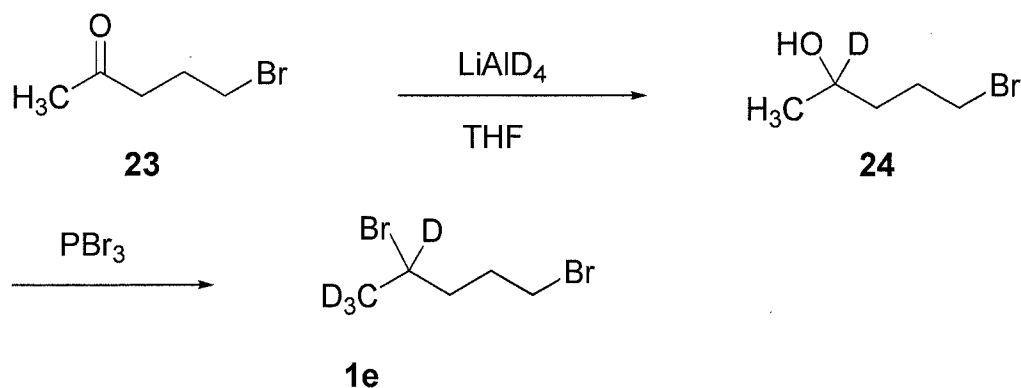
[52] As shown in Scheme 3b, methyl levulinate **8** is treated with LiAlD_4 according to the procedure of Kevan, L et al, J Chem Phys, 1975, 63: 409-416 to give diol **15**, which cyclizes to **16** upon treatment with D_3PO_4 . Ring-opening of **16** with DBr and D_2O in a manner analogous to the procedure of Leonard, NJ et al, J Am Chem Soc, 1952, 74: 917-20 provides **1b**.

Scheme 3c. Preparation of 1,4-dibromo-2,2,3,3-d₄-pentane **1c**.

[53] As shown in Scheme 3c, 2-pentyn-1,4-diol **17** is treated with D₂/PtO₂ according to the procedure of Kevan, L et al, J Chem Phys, 1975, 63: 409-416 to give diol **18**, which cyclizes to **19** upon treatment with H₃PO₄. Ring-opening of **19** with HBr and H₂O in a manner analogous to the procedure of Leonard, NJ et al, J Am Chem Soc, 1952, 74: 917-20 provides **1c**.

Scheme 3d. Preparation of 1,4-dibromo-5,5,5-d₃-pentane **1d**.

[54] As shown in Scheme 3d, aldehyde **20**, obtained as described in Cohen, T et al, Tetrahedron Lett, 1993, 34: 8023-24, is treated with CD₃MgI in a manner analogous to that described by Cohen et al. to give diol **21**, which cyclizes to **22** upon treatment with Nafion[®] NR50. Alternatively, **22** may be prepared from 2-tetrahydrofuroic acid as described in Jeschke, G; et al.; J. Amer. Chem. Soc. 2010, 132(29), 10107-10117. Ring-opening of **22** with HBr and H₂O in a manner analogous to the procedure of Leonard, NJ et al, J Am Chem Soc, 1952, 74: 917-20 provides **1d**.

Scheme 3e. Preparation of 1,4-dibromo-4,5,5,5-d₄-pentane **1e**.

[55] As shown in Scheme 3e, 5-bromo-pentan-2-one **23** is reduced with LiAlD₄ in a manner analogous to that described by Quintard, JP, et al, J Organomet Chem, 1984, 266: 123-38 to afford alcohol **24**, which upon bromination with PBr₃ yields **1e**.

[56] 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 chemical 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.

[57] Additional methods of synthesizing compounds of Formula I or Ia 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, TW 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.

[58] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

COMPOSITIONS

[59] The invention also provides pyrogen-free pharmaceutical compositions comprising an effective amount of a compound of Formula I or Ia (e.g., including any of the formulae herein), or a pharmaceutically acceptable salt of said compound; and 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.

[60] 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.

[61] 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.

[62] 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 United States patent 7,014,866; and United States patent publications 20060094744 and 20060079502.

[63] 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: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins, Baltimore, MD (20th ed. 2000).

[64] 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.

[65] 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.

[66] 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.

[67] 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.

[68] 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.

[69] 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-butanediol. 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.

[70] 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.

[71] 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 JD and Zaffaroni AC, US Patent 6,803,031, assigned to Alexza Molecular Delivery Corporation.

[72] 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.

[73] 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.

[74] 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 US Patents 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 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.

[75] 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.

[76] 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.

[77] 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.

[78] 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.

[79] Where an organ or tissue is accessible because of removal from the subject, 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.

[80] In another embodiment, a composition of this invention further comprises a second therapeutic agent. In one embodiment, the second therapeutic agent is an agent useful in the treatment or prevention of a protozoan infection, in particular malaria caused by *Plasmodium vivax* or *Plasmodium ovale*; or *Pneumocystis* pneumonia.

[81] In one embodiment, the second therapeutic agent is selected from and anti-malarial or an anti-fungal. In a more specific embodiment, the second therapeutic

agent is selected from one or more of quinine, quinacrine, doxycycline hydrate, arteminol, chloroquine, hydroxychloroquine, artemether, artesunate, lumefantrine, halofantrine, mefloquine, artemotil, MMH-8, bulaquine, dihydroartemisinin, piperazine, artesunate, mefloquine, pyrimethamine, sulphalene, sulfamethoxypyrazine, cinchonine, quinidine, cinchonidine, sulfadoxine, atovaquone, proguanil, trimethoprim, amodiaquine, clindamycin and pharmaceutically acceptable salts of the foregoing. In one aspect of this embodiment, the second therapeutic agent is a combination of dihydroartemisinin, piperazine, and trimethoprim. In an alternate aspect, the second therapeutic agent is clindamycin.

[82] 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).

[83] 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 the target disorder.

[84] 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 approximately determined from height and weight of the subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 1970, 537.

[85] In one embodiment, an effective amount of a compound of this invention can range from 0.1 mg/day to 100 mg/day for an adult human. In one embodiment, an effective amount of a compound of this invention can range from 10 mg/day to 100 mg/day. In another embodiment, an effective amount of a compound of this invention can range from 15 mg/day to 50 mg/day. A typical course of treatment for a compound of this invention lasts 7-21 days. In one embodiment, a typical course of treatment lasts 14 days.

[86] 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 subject, 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 Compound 1.

[87] 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.*

[88] 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 or 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

[89] In another embodiment, the invention provides a method of treating or preventing a protozoan infection, in particular malaria caused by *Plasmodium vivax* or *Plasmodium ovale*; or *Pneumocystis pneumonia*, the method comprising administering to a subject in need of such treatment or prevention an effective amount of a compound of Formula I or Ia, or a pharmaceutically acceptable salt of either, or a composition of the invention.

[90] In one particular embodiment, the method of this invention is used to provide a radical cure of vivax malaria, prevent relapse in vivax malaria, or as a preventative measure following the termination of chloroquine phosphate suppressive therapy in a geographical area where vivax malaria is endemic in a subject in need thereof.

[91] In another particular embodiment, the method of this invention is used to treat AIDS-related *Pneumocystitis* pneumonia in a subject in need thereof.

[92] Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

[93] In another embodiment, any of the above methods of treatment comprises the further step of co-administering to the subject in need thereof one or more second therapeutic agents. 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.

[94] In one embodiment, the invention provides a method of treating or preventing a malarial infection comprising the step of co-administering to a subject in need thereof a compound of Formula I or Ia, or a pharmaceutically acceptable salt of said compound, or a pharmaceutical composition comprising a compound of Formula I or Ia; and chloroquine phosphate. In one aspect of this embodiment, the malaria is vivax malaria.

[95] In another embodiment, the invention the invention provides a method of treating or preventing a malarial infection comprising the step of co-administering to a subject in need thereof a compound of Formula I or Ia, or a pharmaceutically acceptable salt of said compound, or a pharmaceutical composition comprising a compound of Formula I or Ia; and a combination of dihydroartemisinin, piperazine, and trimethoprim.

[96] In still another embodiment, the invention the invention provides a method of treating *Pneumocystis* pneumonia comprising the step of co-administering to a subject in need thereof a compound of Formula I or Ia, or a pharmaceutically acceptable salt of said compound, or a pharmaceutical composition comprising a compound of Formula I or Ia; and clindamycin. In one embodiment, the subject is suffering from AIDS.

[97] 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 methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

[98] 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.

[99] 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.

[100] In yet another aspect, the invention provides the use of a compound of Formula I or Ia, or a pharmaceutically acceptable salt of said compound, 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 subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of Formula I or Ia, or a pharmaceutically acceptable salt of said compound, for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

Example 1. Evaluation of Metabolic Stability

[101] **Microsomal Assay:** Human liver microsomes (20 mg/mL) are obtained from Xenotech, LLC (Lenexa, KS). β -nicotinamide adenine dinucleotide phosphate, reduced form (NADPH), magnesium chloride (MgCl_2), and dimethyl sulfoxide (DMSO) are purchased from Sigma-Aldrich.

[102] **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 μM 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 μL aliquot of the 12.5-50 μM 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 μM 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 $^{\circ}\text{C}$, and 50 μL aliquots are removed at 0, 5, 10, 20, and 30 minutes and added to shallow-well 96-well plates which contain 50 μL of ice-cold ACN with internal standard to stop the reactions. The plates are stored at 4 $^{\circ}\text{C}$ for 20 minutes after which 100 μL 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 or Ia and the positive control, 7-ethoxycoumarin (1 μM). Testing is done in triplicate.

[103] **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.

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

$$k = -[\text{slope of linear regression of \% parent remaining(ln) vs incubation time}]$$

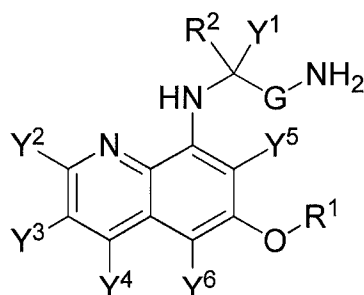
[104] Data analysis is performed using Microsoft Excel Software.

[105] 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.

CLAIMS

What is claimed is:

1. A compound of Formula I:



(I) or a pharmaceutically acceptable la

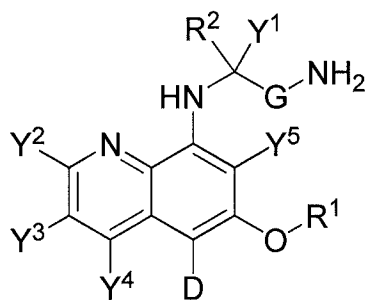
thereof, wherein:

each of R^1 and R^2 is independently selected from $-CH_3$, $-CH_2D$, $-CHD_2$ and $-CD_3$;

each Y is independently selected from hydrogen and deuterium; and

G is n-propylene optionally substituted with 1-6 deuterium, provided that if G is $-CH_2CH_2CD_2-$, $R^1 = R^2 = -CH_3$ and $Y^1 = H$, or if G is $-(CH_2)_3-$, $R^1 = R^2 = -CH_3$ and $Y^1 = D$, then at least one of Y^2 , Y^3 , Y^4 , Y^5 and Y^6 is D, further provided that if G is $-(CH_2)_3-$, $R^1 = R^2 = -CH_3$ and $Y^1 = H$, then at least two of Y^2 , Y^3 , Y^4 , Y^5 and Y^6 is D, wherein “†” represents a portion of G bound to the terminal $-NH_2$ group in the compound.

2. The compound of claim 1 wherein the compound is of Formula Ia:



(Ia) or a pharmaceutically

acceptable salt thereof, wherein:

each of R^1 and R^2 is independently selected from $-CH_3$, $-CH_2D$, $-CHD_2$ and $-CD_3$;

each Y is independently selected from hydrogen and deuterium; and

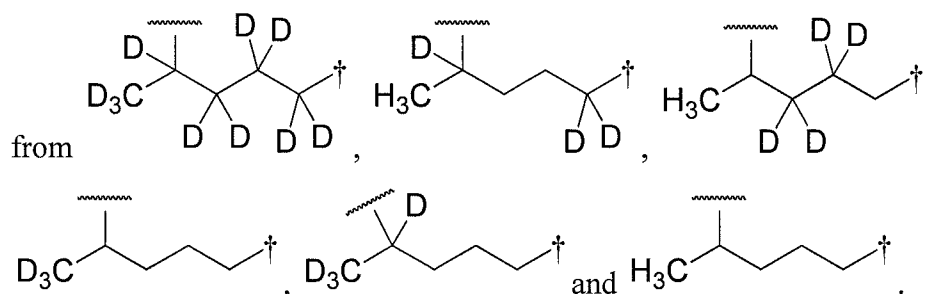
G is n-propylene optionally substituted with 1-6 deuterium, provided that at least one of R^1 , R^2 , G, Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 comprises D.

3. The compound of claim 1 or claim 2, wherein:

G is selected from $-(CD_2)_3-$, $-(CH_2)_3-$, $-CH_2CH_2CD_2-\dagger$ and $-CH_2CD_2CD_2-\dagger$, wherein “ $\dagger$ ” represents a portion of G bound to the terminal $-NH_2$ group in the compound; and

each of R^1 and R^2 is independently selected from $-CD_3$ and $-CH_3$.

4. The compound of claim 3, wherein the moiety $-C(R^2)(Y^1)-G-\dagger$ is selected



5. The compound of any one of claims 1-4, wherein Y^5 is deuterium.
6. The compound of any one of claims 1-4, wherein each of Y^2 , Y^3 , Y^4 and Y^5 are the same.
7. The compound of claim 6, wherein Y^2 , Y^3 , Y^4 , and Y^5 are simultaneously deuterium.
8. The compound of any one of claims 1-7, wherein any atom not designated as deuterium is present at its natural isotopic abundance.
9. The compound of Claim 1 selected from any one of the compounds set forth in the table below:

Cmpd #	R^1	R^2	Y^1	G	Each of Y^2 , Y^3 , Y^4	Each of Y^5 , Y^6
200	$-CH_3$	$-CD_3$	D	$-(CD_2)_3-\dagger$	H	H

Cmpd #	R ¹	R ²	Y ¹	G	Each of Y ² , Y ³ , Y ⁴	Each of Y ⁵ , Y ⁶
201	-CH ₃	-CD ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	H
202	-CH ₃	-CD ₃	D	-CH ₂ CD ₂ CD ₂ -†	H	H
203	-CH ₃	-CD ₃	D	-(CH ₂) ₃ -†	H	H
204	-CH ₃	-CD ₃	H	-(CD ₂) ₃ -†	H	H
205	-CH ₃	-CD ₃	H	-CH ₂ CH ₂ CD ₂ -†	H	H
206	-CH ₃	-CD ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	H
207	-CH ₃	-CD ₃	H	-(CH ₂) ₃ -†	H	H
208	-CD ₃	-CD ₃	D	-(CD ₂) ₃ -†	H	H
209	-CD ₃	-CD ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	H
210	-CD ₃	-CD ₃	D	-CH ₂ CD ₂ CD ₂ -†	H	H
211	-CD ₃	-CD ₃	D	-(CH ₂) ₃ -†	H	H
212	-CD ₃	-CD ₃	H	-(CD ₂) ₃ -†	H	H
213	-CD ₃	-CD ₃	H	-CH ₂ CH ₂ CD ₂ -†	H	H
214	-CD ₃	-CD ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	H
215	-CD ₃	-CD ₃	H	-(CH ₂) ₃ -†	H	H
216	-CH ₃	-CH ₃	D	-(CD ₂) ₃ -†	H	H
217	-CH ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	H
218	-CH ₃	-CH ₃	D	-CH ₂ CD ₂ CD ₂ -†	H	H
219	-CD ₃	-CH ₃	D	-(CD ₂) ₃ -†	H	H
220	-CD ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	H
221	-CD ₃	-CH ₃	D	-CH ₂ CD ₂ CD ₂ -†	H	H
222	-CD ₃	-CH ₃	D	-(CH ₂) ₃ -†	H	H
223	-CD ₃	-CH ₃	H	-(CD ₂) ₃ -†	H	H
224	-CD ₃	-CH ₃	H	-CH ₂ CH ₂ CD ₂ -†	H	H
225	-CD ₃	-CH ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	H
226	-CD ₃	-CH ₃	H	-(CH ₂) ₃ -†	H	H
227	-CH ₃	-CH ₃	H	-(CD ₂) ₃ -†	H	H
228	-CH ₃	-CH ₃	H	-CH ₂ CD ₂ CD ₂ -†	H	H

or a pharmaceutically acceptable salt thereof.

10. The compound of Claim 2 selected from any one of the compounds set forth in the table below:

Cmpd #	R ¹	R ²	Y ¹	G	Each of Y ² , Y ³ , Y ⁴	Y ⁵
100	-CH ₃	-CD ₃	D	-(CD ₂) ₃ -†	D	D
101	-CH ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	D	D
102	-CH ₃	-CH ₃	H	-CD ₂ CD ₂ CH ₂ -†	D	D
103	-CH ₃	-CD ₃	H	-(CH ₂) ₃ -†	D	D
104	-CH ₃	-CD ₃	D	-(CH ₂) ₃ -†	D	D
105	-CH ₃	-CH ₃	H	-(CH ₂) ₃ -†	D	D
106	-CD ₃	-CD ₃	D	-(CD ₂) ₃ -†	D	D
107	-CD ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	D	D
108	-CD ₃	-CH ₃	H	-CD ₂ CD ₂ CH ₂ -†	D	D
109	-CD ₃	-CD ₃	H	-(CH ₂) ₃ -†	D	D
110	-CD ₃	-CD ₃	D	-(CH ₂) ₃ -†	D	D
111	-CD ₃	-CH ₃	H	-(CH ₂) ₃ -†	D	D
112	-CH ₃	-CD ₃	D	-(CD ₂) ₃ -†	H	D
113	-CH ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	D
114	-CH ₃	-CH ₃	H	-CD ₂ CD ₂ CH ₂ -†	H	D
115	-CH ₃	-CD ₃	H	-(CH ₂) ₃ -†	H	D
116	-CH ₃	-CD ₃	D	-(CH ₂) ₃ -†	H	D
117	-CH ₃	-CH ₃	H	-(CH ₂) ₃ -†	H	D
118	-CD ₃	-CD ₃	D	-(CD ₂) ₃ -†	H	D
119	-CD ₃	-CH ₃	D	-CH ₂ CH ₂ CD ₂ -†	H	D
120	-CD ₃	-CH ₃	H	-CD ₂ CD ₂ CH ₂ -†	H	D
121	-CD ₃	-CD ₃	H	-(CH ₂) ₃ -†	H	D
122	-CD ₃	-CD ₃	D	-(CH ₂) ₃ -†	H	D
123	-CD ₃	-CH ₃	H	-(CH ₂) ₃ -†	H	D

or a pharmaceutically acceptable salt thereof.

11. A pyrogen-free pharmaceutical composition comprising a compound of any one of claims 1-10; and a pharmaceutically acceptable carrier.

12. The composition of claim 11, further comprising a second therapeutic agent is selected from an anti-malarial agent or an anti-fungal agent.
13. The composition of claim 12, wherein the second therapeutic agent is selected from one or more of quinine, quinacrine, doxycycline hydrate, arteminol, chloroquine, hydroxychloroquine, artemether, artesunate, lumefantrine, halofantrine, mefloquine, artemotil, MMH-8, bulaquine, dihydroartemisinin, piperazine, artesunate, mefloquine, pyrimethamine, sulphalene, sulfamethoxypyrazine, cinchonine, quinidine, cinchonidine, sulfadoxine, atovaquone, proguanil, trimethoprim, amodiaquine, clindamycin and pharmaceutically acceptable salts of the foregoing.
14. The composition of claim 13, wherein the second therapeutic agent is a combination of dihydroartemisinin, piperazine, and trimethoprim.
15. A method of treating or preventing a protozoan infection in a subject comprising the step of administering to the subject in need thereof a composition of claim 11.
16. The method of claim 15, wherein the protozoan infection is malaria caused by *Plasmodium vivax* or *Plasmodium ovale*; or *Pneumocystis pneumonia*.
17. A method of providing a radical cure of vivax malaria to a subject, preventing relapse in vivax malaria in a subject, or preventing recurrence of vivax malaria in a subject following termination of chloroquine treatment, the method comprising the step of administering to the subject in need thereof a composition of claim 11.
18. The method of any one of claims 15-17, comprising the additional step of co-administering to the subject in need thereof a second therapeutic agent selected from an anti-malarial agent or an anti-fungal agent.

19. The method of claim 18, wherein the protozoan infection is malaria; and the second therapeutic agent is chloroquine phosphate.
20. The method of claim 19, wherein the protozoan infection is vivax malaria.
21. The method of claim 18, wherein the protozoan infection is malaria; and the second therapeutic agent is a combination of dihydroartemisinin, piperazine, and trimethoprim.
22. The method of claim 18, wherein the protozoan infection is *Pneumocystis* pneumonia; and the second therapeutic agent is clindamycin.
23. The method of claim 22, wherein the subject is suffering from AIDS.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/21715

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A01N 43/90 (2011.01)

USPC - 514/306

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

USPC: 514/306

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/313, 235.2; 546/163, 138 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (PGPB,USPT,EPAB,JPAB), Google Scholar, Patentscope

8-aminoquinoline, (RS)-N-(6-methoxyquinolin-8-yl)pentane-1,4-diamine, primaquine, deuterium, deuterated, isotop\$, antimalarial, pharmacokinetic, metabol\$

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	MCCHESNEY et al. Synthesis of site specifically deuterated primaquines II. N-alkyl deuterated primaquines. Journal of Labelled Compounds and Radiopharmaceuticals, April 1984, Vol 21(4), pp 293-298; pg 294	1-3 ----- 4, 9-10
Y	US 6,710,053 B2 (NAICKER et al.) 23 March 2004 (23.03.2004) col 1, ln 20-25; col 4, ln 16-22, ln 30-41; Fig 1-4; col 6, ln 18-26	4, 9-10

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

08 March 2011 (08.03.2011)

Date of mailing of the international search report

05 APR-2011

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 11/21715

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

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

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

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

3. ☒ Claims Nos.: 5-8, 11-23
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.