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(54) Title: PHOSPHOPANTOTHENATE COMPOUNDS

(57) Abstract: The invention relates to phosphopantothenate compounds and pharmaceutical preparations thereof. The invention further relates to methods of treatment using the novel compounds of the invention.



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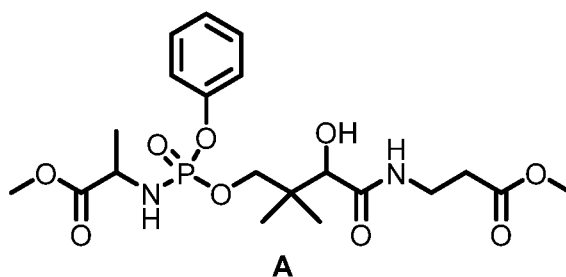
PHOSPHOPANTOTHENATE COMPOUNDS

BACKGROUND OF THE INVENTION

Pantothenate Kinase-Associated Neurodegeneration (PKAN) is a form of neurodegeneration with brain iron accumulation (NBIA) characterized by progressive extrapyramidal dysfunction. PKAN in its classic form causes significant pediatric morbidity and mortality. Atypical PKAN causes morbidity and mortality among adults beginning in the second and third decades of life.

PKAN arises from mutations in the *PANK2* gene, which in humans is the principal isoform expressed in the brain. Other isoforms of pantothenate kinase, which are preferentially expressed in other tissues, are PANK1 α , PANK1 β , and PANK3. The loss of PANK2 activity in the brain impairs or prevents the phosphorylation of pantothenate (also known as Vitamin B₅), which impairs or prevents proper homeostasis of Coenzyme A (CoA) and, in turn, is theorized to cause the symptoms of PKAN.

No safe and effective therapy is known for PKAN. Some have attempted to prepare compounds capable of providing phosphopantothenate; however, the compounds that have been reported were dosed at exceptionally high levels—hundreds of milligrams per kilogram—yet failed to increase brain CoA levels in mouse models. One such compound had the following structure:

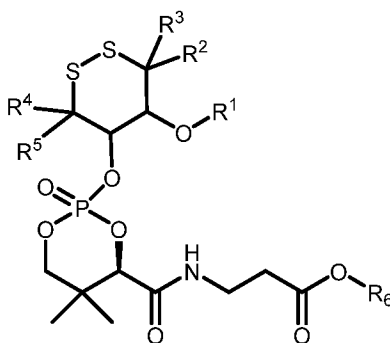


(S.P. Zano, et al., *Correction of a genetic deficiency in pantothenate kinase 1 using phosphopantothenate replacement therapy*, Mol. Genet. Metab. (2015), <http://dx.doi.org/10.1016/j.ymgme.2015.10.011>.)

Thus, there is a need for new therapies for PKAN, and in particular for therapies that can effectively deliver phosphopantothenate to the brain.

SUMMARY OF THE INVENTION

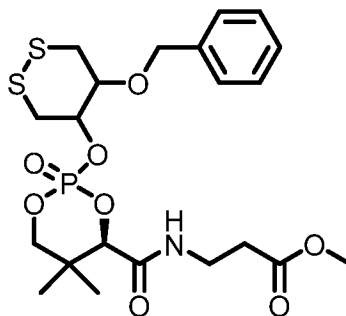
In certain embodiments, the present invention provides compounds having the structure of formula (I):



(I)

or a pharmaceutically acceptable salt and/or prodrug thereof. In the structure of formula (I), R¹ and R⁶ are each independently selected from alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl; and R², R³, R⁴, and R⁵, are each independently selected from H, alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

Exemplary compounds of Formula (I) include the compounds depicted in Table 1 and Compound 1:

**1**

The invention further relates to pharmaceutical compositions of the subject compounds, as well as methods of using these compounds or compositions in the treatment of PKAN.

DETAILED DESCRIPTION OF THE DRAWINGS

Figure 1 shows the results of a plasma stability assay on Compound 2.

Figure 2 shows survival rates in mice dosed with various amounts of HoPan.

Figure 3 shows body weight variation in mice dosed with various amounts of

5 HoPan.

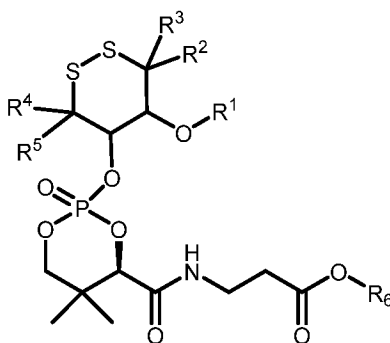
Figure 4 shows survival rates in mice dosed with 100 mg/kg HoPan as well as various amounts of Compound 2.

Figure 5 shows body weight variation in mice dosed with 100 mg/kg HoPan as well as various amounts of Compound 2.

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DETAILED DESCRIPTION OF THE INVENTION

In certain embodiments, the present invention provides compounds having the structure of formula (I):



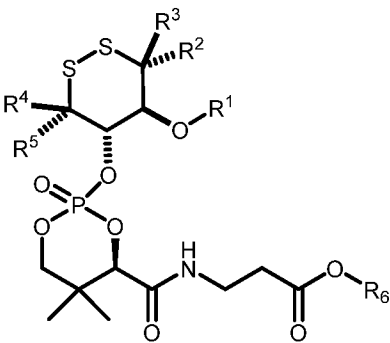
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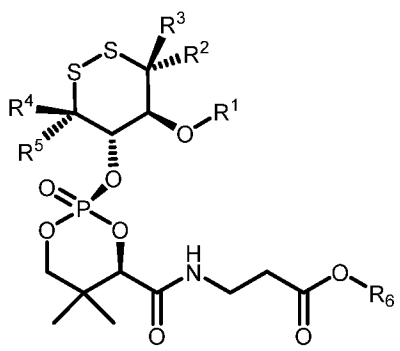
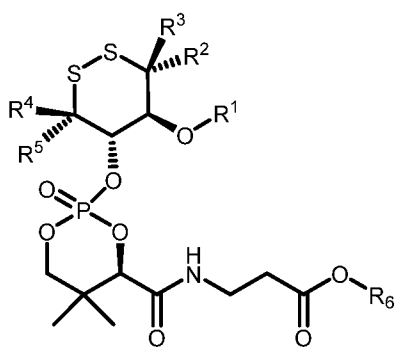
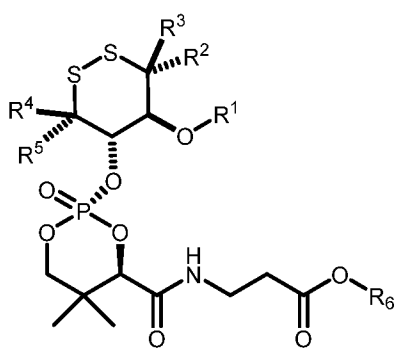
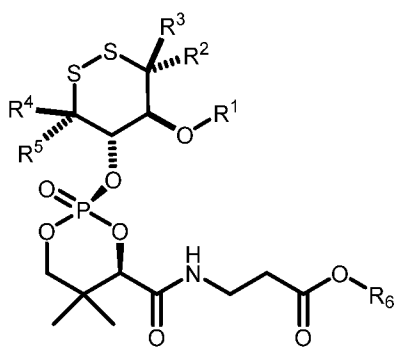
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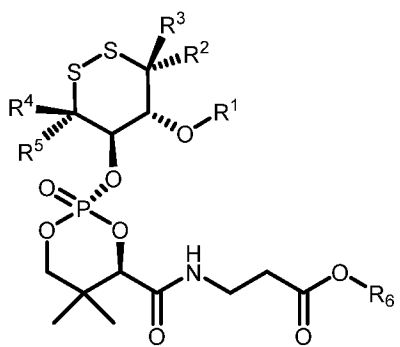
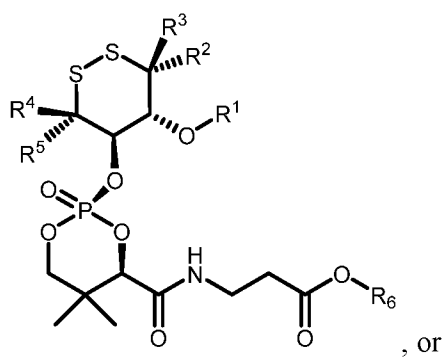
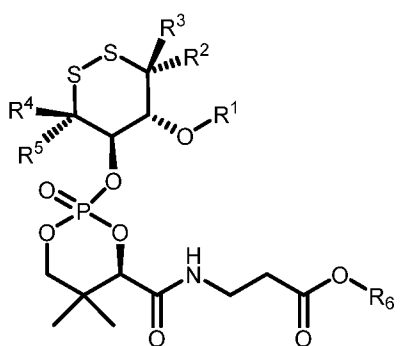
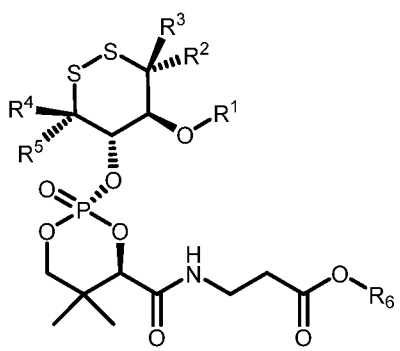
and pharmaceutically acceptable salts and/or prodrugs thereof. In the structure of formula (I), R¹ and R⁶ are each independently selected from H, alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl; R², R³, R⁴, and R⁵ are each independently selected from alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

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In certain such embodiments, the compound has one of the following structures:

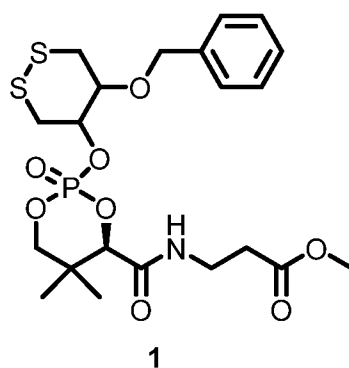




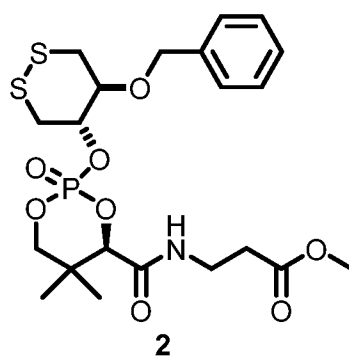


- 5 In certain preferred embodiments of these formulae, R^1 is benzyl; R^2 , R^3 , R^4 , and R^5 are H; and R^6 is methyl.

In further embodiments, the compound is represented by the following structure:



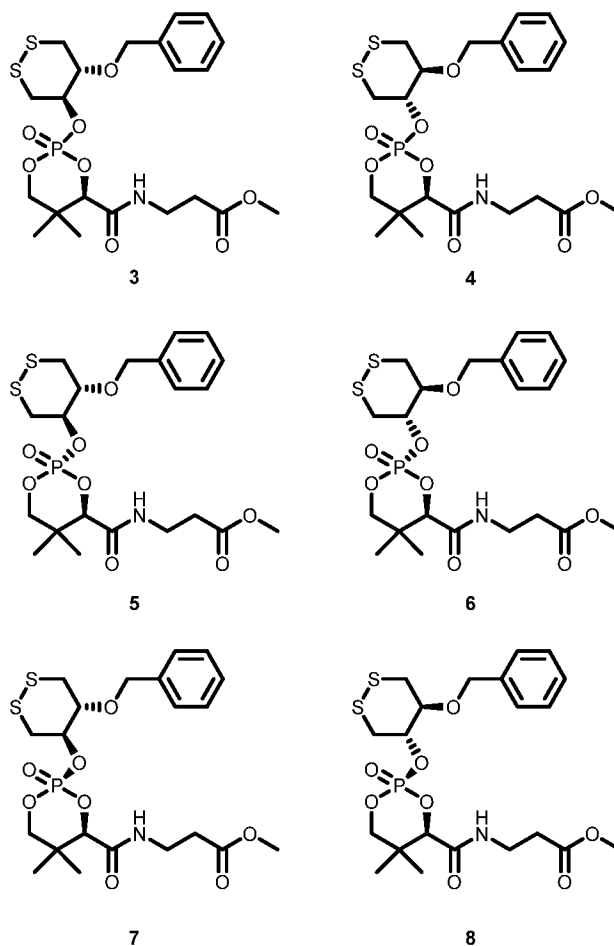
In certain preferred embodiments, the compound has the structure of Compound 2:



- 5 According to these embodiments, the two substituents on the dithiane ring are disposed in the *trans* orientation relative to each other; however, the use of bar bonds (rather than wedge bonds, as in the cyclic phosphate ring) in the structure indicates that their absolute stereochemistry is not specified. That is, compound **2** could be a mixture of (S,S) and (R,R) configurations on the dithiane ring, or could be enriched or substantially
- 10 pure in either diastereomer.

In other embodiments, the invention relates to compounds having the structures depicted in Table 1 and pharmaceutically acceptable salts and prodrugs thereof.

Table 1: Compounds



These compounds can be used to treat neurological disorders or PKAN, or for any
 5 other purpose for which phosphopantothenate is useful in the treatment of disease.

These compounds are expected to have desirable pharmacokinetic properties, because their calculated log P (octanol-water partition), log S (solubility in water), and TPSA (total polar surface area) values all indicate that they will efficiently cross cell membranes. Those calculated values are given in Table 2.

10

Table 2:

Compound	log P	S log P	TPSA
1	2.4	2.8	109

In certain embodiments, compounds of the invention are prodrugs of the compounds of Table 1, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate, or a carboxylic acid present in the parent compound is presented as an ester. In

certain such embodiments, the prodrug is metabolized to the active parent compound in vivo (e.g., the ester is hydrolyzed to the corresponding hydroxyl or carboxylic acid).

In certain embodiments, compounds of the invention may be racemic. In certain embodiments, compounds of the invention may be enriched in one enantiomer. For example, a compound of the invention may have greater than 30% ee, 40% ee, 50% ee, 60% ee, 70% ee, 80% ee, 90% ee, or even 95% or greater ee. In certain embodiments, compounds of the invention may have more than one stereocenter. In certain such embodiments, compounds of the invention may be enriched in one or more diastereomers. For example, a compound of the invention may have greater than 30% de, 40% de, 50% de, 60% de, 70% de, 80% de, 90% de, or even 95% or greater de.

In certain embodiments, the present invention relates to methods of treatment with a compound selected from Table 1, or a pharmaceutically acceptable salt thereof. In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one enantiomer of a compound (e.g., of a compound selected from Table 1). An enantiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 90, 95, or even 99 mol percent. In certain embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than 1% as compared to the amount of the other enantiomer, *e.g.*, in the composition or compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grams of a second enantiomer, it would be said to contain 98 mol percent of the first enantiomer and only 2% of the second enantiomer.

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (e.g., of a compound selected from Table 1). A diastereomerically enriched mixture may comprise, for example, at least 60 mol percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

In certain embodiments, the present invention relates to methods of treatment with a compound selected from Table 1, or a pharmaceutically acceptable salt thereof. In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one enantiomer of a compound (e.g., of a compound selected from Table 1). An enantiomerically enriched mixture may comprise, for example, at least 60 mol percent of one enantiomer, or more preferably at least 75, 90, 95, or even 99 mol percent. In certain

embodiments, the compound enriched in one enantiomer is substantially free of the other enantiomer, wherein substantially free means that the substance in question makes up less than 10%, or less than 5%, or less than 4%, or less than 3%, or less than 2%, or less than 1% as compared to the amount of the other enantiomer, *e.g.*, in the composition or

5 compound mixture. For example, if a composition or compound mixture contains 98 grams of a first enantiomer and 2 grams of a second enantiomer, it would be said to contain 98 mol percent of the first enantiomer and only 2% of the second enantiomer.

In certain embodiments, the therapeutic preparation may be enriched to provide predominantly one diastereomer of a compound (*e.g.*, of a compound selected from Table 1). A diastereomerically enriched mixture may comprise, for example, at least 60 mol
10 percent of one diastereomer, or more preferably at least 75, 90, 95, or even 99 mol percent.

In certain embodiments, the present invention provides a pharmaceutical preparation suitable for use in a human patient, comprising any of the compounds shown above (*e.g.*, a compound of the invention, such as a compound selected from Table 1), and one or more
15 pharmaceutically acceptable excipients. In certain embodiments, the pharmaceutical preparations may be for use in treating or preventing a condition or disease as described herein. In certain embodiments, the pharmaceutical preparations have a low enough pyrogen activity to be suitable for use in a human patient.

Compounds of any of the above structures may be used in the manufacture of
20 medicaments for the treatment of any diseases or conditions disclosed herein.

Definitions

The term “acyl” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)-, preferably alkylC(O)-.

The term “acylamino” is art-recognized and refers to an amino group substituted
25 with an acyl group and may be represented, for example, by the formula hydrocarbylC(O)NH-.

The term “acyloxy” is art-recognized and refers to a group represented by the general formula hydrocarbylC(O)O-, preferably alkylC(O)O-.

The term “alkoxy” refers to an alkyl group, preferably a lower alkyl group, having
30 an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like.

The term “alkoxyalkyl” refers to an alkyl group substituted with an alkoxy group and may be represented by the general formula alkyl-O-alkyl.

The term "alkenyl", as used herein, refers to an aliphatic group containing at least one double bond and is intended to include both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the alkenyl group. Such substituents may occur on one or more carbons that are included or not included in one or more double bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed below, except where stability is prohibitive. For example, substitution of alkenyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

An "alkyl" group or "alkane" is a straight chained or branched non-aromatic hydrocarbon which is completely saturated. Typically, a straight chained or branched alkyl group has from 1 to about 20 carbon atoms, preferably from 1 to about 10 unless otherwise defined. Examples of straight chained and branched alkyl groups include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, tert-butyl, pentyl, hexyl, pentyl and octyl. A C₁-C₆ straight chained or branched alkyl group is also referred to as a "lower alkyl" group.

Moreover, the term "alkyl" (or "lower alkyl") as used throughout the specification, examples, and claims is intended to include both "unsubstituted alkyls" and "substituted alkyls", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents, if not otherwise specified, can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxy carbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CF₃, -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls can be further substituted with alkyls, alkenyls, alkoxy, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CF₃, -CN, and the like.

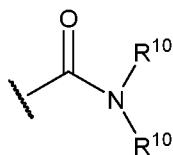
The term “C_{x-y}” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups that contain from x to y carbons in the chain. For example, the term “C_{x-y}alkyl” refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups that contain from x to y carbons in the chain, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. C₀ alkyl indicates a hydrogen where the group is in a terminal position, a bond if internal. The terms “C_{2-y}alkenyl” and “C_{2-y}alkynyl” refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

The term “alkylamino”, as used herein, refers to an amino group substituted with at least one alkyl group.

The term “alkylthio”, as used herein, refers to a thiol group substituted with an alkyl group and may be represented by the general formula alkylS-.

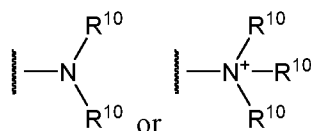
The term “alkynyl”, as used herein, refers to an aliphatic group containing at least one triple bond and is intended to include both “unsubstituted alkynyls” and “substituted alkynyls”, the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the alkynyl group. Such substituents may occur on one or more carbons that are included or not included in one or more triple bonds. Moreover, such substituents include all those contemplated for alkyl groups, as discussed above, except where stability is prohibitive. For example, substitution of alkynyl groups by one or more alkyl, carbocyclyl, aryl, heterocyclyl, or heteroaryl groups is contemplated.

The term “amide”, as used herein, refers to a group



wherein each R¹⁰ independently represent a hydrogen or hydrocarbonyl group, or two R¹⁰ are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

The terms “amine” and “amino” are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by



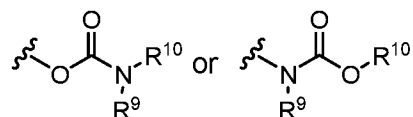
wherein each R¹⁰ independently represents a hydrogen or a hydrocarbonyl group, or two R¹⁰ are taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure.

5 The term “aminoalkyl”, as used herein, refers to an alkyl group substituted with an amino group.

 The term “aralkyl”, as used herein, refers to an alkyl group substituted with an aryl group.

 The term “aryl” as used herein include substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. Preferably the ring is a 5- to 7-membered ring, more preferably a 6-membered ring. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like.

 The term “carbamate” is art-recognized and refers to a group



wherein R⁹ and R¹⁰ independently represent hydrogen or a hydrocarbonyl group, such as an alkyl group, or R⁹ and R¹⁰ taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

 The terms “carbocycle”, and “carbocyclic”, as used herein, refers to a saturated or unsaturated ring in which each atom of the ring is carbon. The term carbocycle includes both aromatic carbocycles and non-aromatic carbocycles. Non-aromatic carbocycles include both cycloalkane rings, in which all carbon atoms are saturated, and cycloalkene rings, which contain at least one double bond. “Carbocycle” includes 5-7 membered monocyclic and 8-12 membered bicyclic rings. Each ring of a bicyclic carbocycle may be selected from saturated, unsaturated and aromatic rings. Carbocycle includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused carbocycle” refers to a bicyclic carbocycle in which each of the rings shares

two adjacent atoms with the other ring. Each ring of a fused carbocycle may be selected from saturated, unsaturated and aromatic rings. In an exemplary embodiment, an aromatic ring, e.g., phenyl, may be fused to a saturated or unsaturated ring, e.g., cyclohexane, cyclopentane, or cyclohexene. Any combination of saturated, unsaturated and aromatic bicyclic rings, as valence permits, is included in the definition of carbocyclic. Exemplary “carbocycles” include cyclopentane, cyclohexane, bicyclo[2.2.1]heptane, 1,5-cyclooctadiene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]oct-3-ene, naphthalene and adamantane. Exemplary fused carbocycles include decalin, naphthalene, 1,2,3,4-tetrahydronaphthalene, bicyclo[4.2.0]octane, 4,5,6,7-tetrahydro-1H-indene and bicyclo[4.1.0]hept-3-ene. “Carbocycles” may be substituted at any one or more positions capable of bearing a hydrogen atom.

A “cycloalkyl” group is a cyclic hydrocarbon which is completely saturated. “Cycloalkyl” includes monocyclic and bicyclic rings. Typically, a monocyclic cycloalkyl group has from 3 to about 10 carbon atoms, more typically 3 to 8 carbon atoms unless otherwise defined. The second ring of a bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. Cycloalkyl includes bicyclic molecules in which one, two or three or more atoms are shared between the two rings. The term “fused cycloalkyl” refers to a bicyclic cycloalkyl in which each of the rings shares two adjacent atoms with the other ring. The second ring of a fused bicyclic cycloalkyl may be selected from saturated, unsaturated and aromatic rings. A “cycloalkenyl” group is a cyclic hydrocarbon containing one or more double bonds.

The term “carbocyclalkyl”, as used herein, refers to an alkyl group substituted with a carbocycle group.

The term “carbonate” is art-recognized and refers to a group $-\text{OCO}_2\text{-R}^{10}$, wherein R^{10} represents a hydrocarbyl group.

The term “carboxy”, as used herein, refers to a group represented by the formula $-\text{CO}_2\text{H}$.

The term “ester”, as used herein, refers to a group $-\text{C}(\text{O})\text{OR}^{10}$ wherein R^{10} represents a hydrocarbyl group.

The term “ether”, as used herein, refers to a hydrocarbyl group linked through an oxygen to another hydrocarbyl group. Accordingly, an ether substituent of a hydrocarbyl group may be hydrocarbyl-O-. Ethers may be either symmetrical or unsymmetrical. Examples of ethers include, but are not limited to, heterocycle-O-heterocycle and aryl-O-

heterocycle. Ethers include “alkoxyalkyl” groups, which may be represented by the general formula alkyl-O-alkyl.

The terms “halo” and “halogen” as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

5 The terms “hetaralkyl” and “heteroaralkyl”, as used herein, refers to an alkyl group substituted with a hetaryl group.

The term “heteroalkyl”, as used herein, refers to a saturated or unsaturated chain of carbon atoms and at least one heteroatom, wherein no two heteroatoms are adjacent.

10 The terms “heteroaryl” and “hetaryl” include substituted or unsubstituted aromatic single ring structures, preferably 5- to 7-membered rings, more preferably 5- to 6-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heteroaryl” and “hetaryl” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is
15 heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like.

20 The term “heteroatom” as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

25 The terms “heterocyclyl”, “heterocycle”, and “heterocyclic” refer to substituted or unsubstituted non-aromatic ring structures, preferably 3- to 10-membered rings, more preferably 3- to 7-membered rings, whose ring structures include at least one heteroatom, preferably one to four heteroatoms, more preferably one or two heteroatoms. The terms “heterocyclyl” and “heterocyclic” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heterocyclyl groups include, for example, piperidine, piperazine, pyrrolidine, morpholine, lactones, lactams, and
30 the like.

The term “heterocyclylalkyl”, as used herein, refers to an alkyl group substituted with a heterocycle group.

The term “hydrocarbyl”, as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocyclyl, alkyl, alkenyl, alkynyl, and combinations thereof.

The term “hydroxyalkyl”, as used herein, refers to an alkyl group substituted with a hydroxy group.

The term “lower” when used in conjunction with a chemical moiety, such as, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy is meant to include groups where there are ten or fewer non-hydrogen atoms in the substituent, preferably six or fewer. A “lower alkyl”, for example, refers to an alkyl group that contains ten or fewer carbon atoms, preferably six or fewer. In certain embodiments, acyl, acyloxy, alkyl, alkenyl, alkynyl, or alkoxy substituents defined herein are respectively lower acyl, lower acyloxy, lower alkyl, lower alkenyl, lower alkynyl, or lower alkoxy, whether they appear alone or in combination with other substituents, such as in the recitations hydroxyalkyl and aralkyl (in which case, for example, the atoms within the aryl group are not counted when counting the carbon atoms in the alkyl substituent).

The terms “polycyclyl”, “polycycle”, and “polycyclic” refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls) in which two or more atoms are common to two adjoining rings, e.g., the rings are “fused rings”. Each of the rings of the polycycle can be substituted or unsubstituted. In certain embodiments, each ring of the polycycle contains from 3 to 10 atoms in the ring, preferably from 5 to 7.

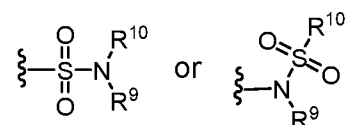
The term “silyl” refers to a silicon moiety with three hydrocarbyl moieties attached thereto.

The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation

such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include any substituents described herein, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that substituents can themselves be substituted, if appropriate. Unless specifically stated as “unsubstituted,” references to chemical moieties herein are understood to include substituted variants. For example, reference to an “aryl” group or moiety implicitly includes both substituted and unsubstituted variants.

The term “sulfate” is art-recognized and refers to the group $-\text{OSO}_3\text{H}$, or a pharmaceutically acceptable salt thereof.

The term “sulfonamide” is art-recognized and refers to the group represented by the general formulae



wherein R^9 and R^{10} independently represents hydrogen or hydrocarbyl, such as alkyl, or R^9 and R^{10} taken together with the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

The term “sulfoxide” is art-recognized and refers to the group $-\text{S}(\text{O})-\text{R}^{10}$, wherein R^{10} represents a hydrocarbyl.

The term “sulfonate” is art-recognized and refers to the group SO_3H , or a pharmaceutically acceptable salt thereof.

The term “sulfone” is art-recognized and refers to the group $-S(O)_2-R^{10}$, wherein R^{10} represents a hydrocarbyl.

The term “thioalkyl”, as used herein, refers to an alkyl group substituted with a thiol group.

5 The term “thioester”, as used herein, refers to a group $-C(O)SR^{10}$ or $-SC(O)R^{10}$ wherein R^{10} represents a hydrocarbyl.

The term “thioether”, as used herein, is equivalent to an ether, wherein the oxygen is replaced with a sulfur.

The term “urea” is art-recognized and may be represented by the general formula



wherein R^9 and R^{10} independently represent hydrogen or a hydrocarbyl, such as alkyl, or either occurrence of R^9 taken together with R^{10} and the intervening atom(s) complete a heterocycle having from 4 to 8 atoms in the ring structure.

“Protecting group” refers to a group of atoms that, when attached to a reactive functional group in a molecule, mask, reduce or prevent the reactivity of the functional group. Typically, a protecting group may be selectively removed as desired during the course of a synthesis. Examples of protecting groups can be found in Greene and Wuts, *Protective Groups in Organic Chemistry*, 3rd Ed., 1999, John Wiley & Sons, NY and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8, 1971-1996, John Wiley & Sons, NY. Representative nitrogen protecting groups include, but are not limited to, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (“CBZ”), tert-butoxycarbonyl (“Boc”), trimethylsilyl (“TMS”), 2-trimethylsilyl-ethanesulfonyl (“TES”), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (“Fmoc”), nitro-veratryloxycarbonyl (“NVOC”) and the like. Representative hydroxylprotecting groups include, but are not limited to, those where the hydroxyl group is either acylated (esterified) or alkylated such as benzyl and trityl ethers, as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers (e.g., TMS or TIPS groups), glycol ethers, such as ethylene glycol and propylene glycol derivatives and allyl ethers.

As used herein, a therapeutic that “prevents” a disorder or condition refers to a compound that, in a statistical sample, reduces the occurrence of the disorder or condition in the treated sample relative to an untreated control sample, or delays the onset or reduces the severity of one or more symptoms of the disorder or condition relative to the untreated

control sample. For example, a compound that prevents epilepsy may reduce the frequency of seizures and/or reduce the severity of seizures.

The term “treating” includes prophylactic and/or therapeutic treatments. The term “prophylactic or therapeutic” treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The phrases “conjoint administration” and “administered conjointly” refer to any form of administration of two or more different therapeutic compounds such that the second compound is administered while the previously administered therapeutic compound is still effective in the body (e.g., the two compounds are simultaneously effective in the patient, which may include synergistic effects of the two compounds). For example, the different therapeutic compounds can be administered either in the same formulation or in a separate formulation, either concomitantly or sequentially. In certain embodiments, the different therapeutic compounds can be administered within one hour, 12 hours, 24 hours, 36 hours, 48 hours, 72 hours, or a week of one another. Thus, an individual who receives such treatment can benefit from a combined effect of different therapeutic compounds.

The term “prodrug” is intended to encompass compounds which, under physiologic conditions, are converted into the therapeutically active agents of the present invention (e.g., a compound selected from Table 1). A common method for making a prodrug is to include one or more selected moieties which are hydrolyzed under physiologic conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal. For example, esters or carbonates (e.g., esters or carbonates of alcohols or carboxylic acids) are preferred prodrugs of the present invention. In certain embodiments, some or all of the compounds selected from Table 1 in a formulation represented above can be replaced with the corresponding suitable prodrug, e.g., wherein a hydroxyl in the parent compound is presented as an ester or a carbonate or carboxylic acid present in the parent compound is presented as an ester.

Uses of the Compounds

In some embodiments, the compounds of the present invention, i.e., the compounds of Formula (I) and/or the compounds of Table 1, may be used to treat neurological disorders. In certain embodiments, they may be used to treat PKAN.

Pharmaceutical Compositions

5 The compositions and methods of the present invention may be utilized to treat an individual in need thereof. In certain embodiments, the individual is a mammal such as a human, or a non-human mammal. When administered to an animal, such as a human, the composition or the compound is preferably administered as a pharmaceutical composition comprising, for example, a compound of the invention and a pharmaceutically acceptable
10 carrier. Pharmaceutically acceptable carriers are well known in the art and include, for example, aqueous solutions such as water or physiologically buffered saline or other solvents or vehicles such as glycols, glycerol, oils such as olive oil, or injectable organic esters. In preferred embodiments, when such pharmaceutical compositions are for human administration, particularly for invasive routes of administration (i.e., routes, such as
15 injection or implantation, that circumvent transport or diffusion through an epithelial barrier), the aqueous solution is pyrogen-free, or substantially pyrogen-free. The excipients can be chosen, for example, to effect delayed release of an agent or to selectively target one or more cells, tissues or organs. The pharmaceutical composition can be in dosage unit form such as tablet, capsule (including sprinkle capsule and gelatin capsule), granule,
20 lyophile for reconstitution, powder, solution, syrup, suppository, injection or the like. The composition can also be present in a transdermal delivery system, e.g., a skin patch. The composition can also be present in a solution suitable for topical administration, such as an eye drop.

 A pharmaceutically acceptable carrier can contain physiologically acceptable agents
25 that act, for example, to stabilize, increase solubility or to increase the absorption of a compound such as a compound of the invention. Such physiologically acceptable agents include, for example, carbohydrates, such as glucose, sucrose or dextrans, antioxidants, such as ascorbic acid or glutathione, chelating agents, low molecular weight proteins or other stabilizers or excipients. The choice of a pharmaceutically acceptable carrier,
30 including a physiologically acceptable agent, depends, for example, on the route of administration of the composition. The preparation or pharmaceutical composition can be a selfemulsifying drug delivery system or a selfmicroemulsifying drug delivery system. The pharmaceutical composition (preparation) also can be a liposome or other polymer matrix,

which can have incorporated therein, for example, a compound of the invention. Liposomes, for example, which comprise phospholipids or other lipids, are nontoxic, physiologically acceptable and metabolizable carriers that are relatively simple to make and administer.

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

10 The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as
15 pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil,
20 olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic
25 compatible substances employed in pharmaceutical formulations.

A pharmaceutical composition (preparation) can be administered to a subject by any of a number of routes of administration including, for example, orally (for example, drenches as in aqueous or non-aqueous solutions or suspensions, tablets, capsules (including sprinkle capsules and gelatin capsules), boluses, powders, granules, pastes for
30 application to the tongue); absorption through the oral mucosa (e.g., sublingually); anally, rectally or vaginally (for example, as a pessary, cream or foam); parenterally (including intramuscularly, intravenously, subcutaneously or intrathecally as, for example, a sterile solution or suspension); nasally; intraperitoneally; subcutaneously; transdermally (for

example as a patch applied to the skin); and topically (for example, as a cream, ointment or spray applied to the skin, or as an eye drop). The compound may also be formulated for inhalation. In certain embodiments, a compound may be simply dissolved or suspended in sterile water. Details of appropriate routes of administration and compositions suitable for same can be found in, for example, U.S. Pat. Nos. 6,110,973, 5,763,493, 5,731,000, 5,541,231, 5,427,798, 5,358,970 and 4,172,896, as well as in patents cited therein.

The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 1 percent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

Methods of preparing these formulations or compositions include the step of bringing into association an active compound, such as a compound of the invention, with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules (including sprinkle capsules and gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), lyophile, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. Compositions or compounds may also be administered as a bolus, electuary or paste.

To prepare solid dosage forms for oral administration (capsules (including sprinkle capsules and gelatin capsules), tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as

sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) complexing agents, such as, modified and unmodified cyclodextrins; and (11) coloring agents. In the case of capsules (including sprinkle capsules and gelatin capsules), tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions, such as dragees, capsules (including sprinkle capsules and gelatin capsules), pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they

release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the
5 above-described excipients.

Liquid dosage forms useful for oral administration include pharmaceutically acceptable emulsions, lyophiles for reconstitution, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents,
10 cyclodextrins and derivatives thereof, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

15 Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan
20 esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions for rectal, vaginal, or urethral administration may be presented as a suppository, which may be prepared by mixing one or more active compounds with one or more suitable nonirritating excipients or carriers
25 comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the pharmaceutical compositions for administration to the mouth may be presented as a mouthwash, or an oral spray, or an oral ointment.

30 Alternatively or additionally, compositions can be formulated for delivery via a catheter, stent, wire, or other intraluminal device. Delivery via such devices may be especially useful for delivery to the bladder, urethra, ureter, rectum, or intestine.

Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to an active compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the active compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention. Exemplary ophthalmic formulations are described in U.S. Publication Nos. 2005/0080056, 2005/0059744, 2005/0031697 and 2005/004074 and U.S. Patent No. 6,583,124, the contents of which are incorporated herein by reference. If desired, liquid ophthalmic formulations have properties similar to that of lacrimal fluids, aqueous humor or vitreous humor or are compatible with such fluids. A preferred route of administration is local administration (*e.g.*, topical administration, such as eye drops, or administration via an implant).

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial,

intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion. Pharmaceutical compositions suitable for parenteral administration comprise one or more active compounds in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution, which, in turn, may depend upon crystal size and crystalline form.

Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsulated matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide.

Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible
5 with body tissue.

For use in the methods of this invention, active compounds can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

Methods of introduction may also be provided by rechargeable or biodegradable
10 devices. Various slow release polymeric devices have been developed and tested *in vivo* in recent years for the controlled delivery of drugs, including proteinaceous biopharmaceuticals. A variety of biocompatible polymers (including hydrogels), including both biodegradable and non-degradable polymers, can be used to form an implant for the sustained release of a compound at a particular target site.

15 Actual dosage levels of the active ingredients in the pharmaceutical compositions may be varied so as to obtain an amount of the active ingredient that is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the
20 activity of the particular compound or combination of compounds employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound(s) being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound(s) employed, the age, sex, weight, condition, general health and prior medical
25 history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the therapeutically effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the pharmaceutical composition or compound at levels lower than that required in order to achieve the desired
30 therapeutic effect and gradually increase the dosage until the desired effect is achieved. By “therapeutically effective amount” is meant the concentration of a compound that is sufficient to elicit the desired therapeutic effect. It is generally understood that the effective amount of the compound will vary according to the weight, sex, age, and medical history of

the subject. Other factors which influence the effective amount may include, but are not limited to, the severity of the patient's condition, the disorder being treated, the stability of the compound, and, if desired, another type of therapeutic agent being administered with the compound of the invention. A larger total dose can be delivered by multiple
5 administrations of the agent. Methods to determine efficacy and dosage are known to those skilled in the art (Isselbacher *et al.* (1996) Harrison's Principles of Internal Medicine 13 ed., 1814-1882, herein incorporated by reference).

In general, a suitable daily dose of an active compound used in the compositions and methods of the invention will be that amount of the compound that is the lowest dose
10 effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above.

If desired, the effective daily dose of the active compound may be administered as one, two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. In certain embodiments of
15 the present invention, the active compound may be administered two or three times daily. In preferred embodiments, the active compound will be administered once daily.

The patient receiving this treatment is any animal in need, including primates, in particular humans, and other mammals such as equines, cattle, swine and sheep; and poultry and pets in general.

20 In certain embodiments, compounds of the invention may be used alone or conjointly administered with another type of therapeutic agent.

This invention includes the use of pharmaceutically acceptable salts of compounds of the invention in the compositions and methods of the present invention. In certain embodiments, contemplated salts of the invention include, but are not limited to, alkyl,
25 dialkyl, trialkyl or tetra-alkyl ammonium salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, L-arginine, benenthamine, benzathine, betaine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)ethanol, ethanolamine, ethylenediamine, N-methylglucamine, hydrabamine, 1H-imidazole, lithium, L-lysine, magnesium, 4-(2-hydroxyethyl)morpholine, piperazine,
30 potassium, 1-(2-hydroxyethyl)pyrrolidine, sodium, triethanolamine, tromethamine, and zinc salts. In certain embodiments, contemplated salts of the invention include, but are not limited to, Na, Ca, K, Mg, Zn or other metal salts.

The pharmaceutically acceptable acid addition salts can also exist as various solvates, such as with water, methanol, ethanol, dimethylformamide, and the like. Mixtures of such solvates can also be prepared. The source of such solvate can be from the solvent of crystallization, inherent in the solvent of preparation or crystallization, or adventitious to such solvent.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

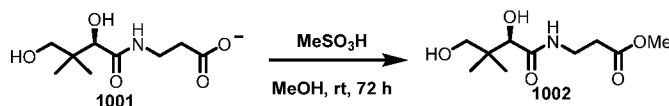
Examples of pharmaceutically acceptable antioxidants include: (1) water-soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

EXAMPLES

Example 1: Synthetic Protocols

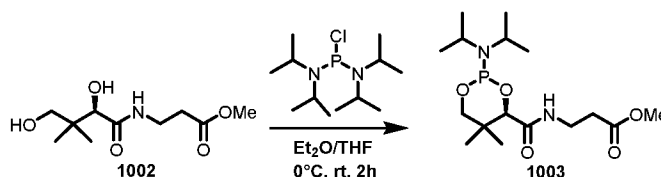
Compound 1002. Methyl pantothenate.



Calcium D- pantothenate hydrate **1001** (107 g, 0.22 mol) was dissolved in 900 ml of methanol and treated with methanesulfonic acid (35 ml, 0.54 mol) dropwise at room temperature and with vigorous stirring. The mixture was stirred at room temperature for 72 hours, then treated with 10 g NaHCO₃. After 1 hour stirring, the mixture was filtered off and the filtrate was stripped of the solvent under the vacuum. The residue was dissolved in 800 ml of EtOAc, 10 g of MgSO₄ was added and this mixture was stirred for 20h. Filtration and

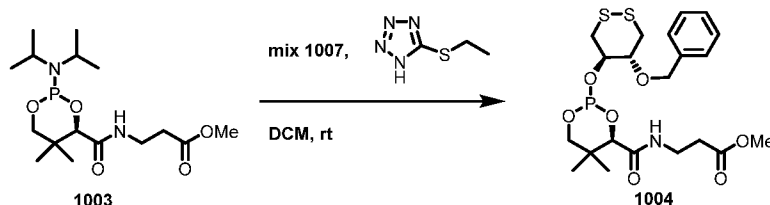
removal of solvent under the vacuum provided 80 g of clear syrup, NMR: 85% purity. A portion of product was purified by flash-chromatography with ether/THF, NMR >95%.

Compound 1003. Methyl *N*-{[(4*R*)-2-(diisopropylamino)-5,5-dimethyl-1,3,2-dioxaphosphinan-4-yl]carbonyl}-β-alaninate.



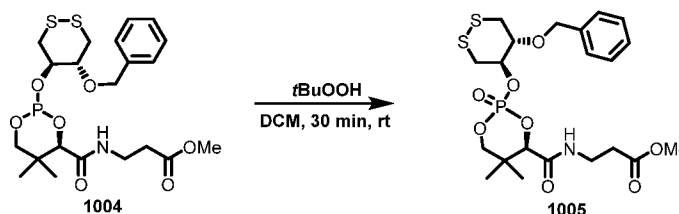
Mixture of **1002** (2.0 g, 0.0086 mol) and Et₃N (1.3 ml, 0.0091 mol) in Et₂O/THF was added dropwise to suspension of bis(diisopropylamino)chlorophosphine **A** (2.3 g, 0.0086 mol) in 30 ml of dry Et₂O at 0°C. The mixture was stirred at 0°C for 1h and at room temperature for 1h. After stirring, the mixture was filtered off and the filtrate was stripped of solvent at 30°C under the vacuum. The residue was purified by flash-chromatography with benzene, NMR: >90% purity. The yield of **1003** was 29%.

Compound 1004. Methyl *N*-[[(4*R*)-2-{[(4*S*,5*R*)-5-(benzyloxy)-1,2-dithian-4-yl]oxy}-5,5-dimethyl-1,3,2-dioxaphosphinan-4-yl]carbonyl]-β-alaninate.



Mixture of **1003** (900 mg, 2.48 mmol), mix of alcohol **1007** (660 mg, 2.72 mmol) and 5-(ethylthio)-1*H*-tetrazole (160 mg, 1.22 mmol) in dichloromethane (DCM) was stirred at room temperature for 30 min (control by TLC). The pure product **1004** was obtained after flash-chromatography with DCM/Et₂O, NMR: >95% purity. The yield of **1004** was 50%.

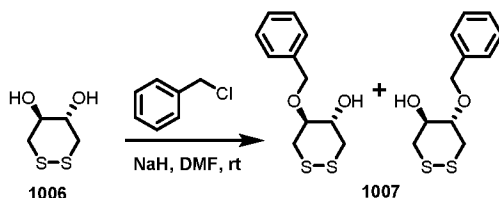
Compound 1005. Methyl *N*-[[(4*R*)-2-{[(4*S*,5*R*)-5-(benzyloxy)-1,2-dithian-4-yl]oxy}-5,5-dimethyl-2-oxido-1,3,2-dioxaphosphinan-4-yl]carbonyl]-β-alaninate.



To a solution of **1004** (630 mg, 1.25 mmol) was added *tert*-butylhydroperoxide (125 mg, 1.25 mmol) and reaction mixture was stirred at room temperature for 30 min (control by TLC). The pure product **1005** was obtained after flash-chromatography with DCM/Et₂O and HPLC, NMR: >95%. The yield of **1005** was 70%.

5

Compound 1007. Mixture of (4S,5R)-5-(Benzyloxy)-1,2-dithian-4-ol and (4R,5S)-5-(Benzyloxy)-1,2-dithian-4-ol.



A sodium hydride-60% in oil (0.29 g, 0.0072 mol) was added to a solution of trans-4,5-dihydroxy-1,2-dithiane **1006** (1.0 g, 0.0066 mol) in dimethylformamide (20 ml) and stirred at room temperature for 1 hour. Benzyl chloride (0.91 g, 0.0072 mol) was added and the reaction mixture was stirred at room temperature for 16h. The reaction mixture was dissolved in water. The aqueous layer was extracted with ether and the combined organic phases were dried Na₂SO₄. The solvent was removed in *vacuo* and the product was purified by silica gel column chromatography with DCM, DCM/ether. The yield of **1007** was 35%.

15

Example 2: Plasma Stability Assay

Compounds were assayed for plasma stability as follows.

1 μ M of subject compound was incubated in duplicates in human and mouse plasma at 37°C. Aliquots were taken at 0, 0.083, 0.25, 0.5, 0.75 and 1 hour. After protein precipitation with MeCN, samples were analyzed by LC-MS/MS.

20

The results of the plasma stability assay are given in Figure 1 and Table 3.

Table 3: Plasma Stability

	Time (h)	Compound 2 Percent Remaining (SD) (n=2)	Compound A Percent Remaining (SD) (n=2)
Mouse	0.083	95% (6.0)	1% (0.6)
	0.25	103% (0.7)	1% (0.0)
	0.5	104% (2.9)	1% (0.0)

	0.75	101% (4.4)	1% (0.1)
	1	100% (3.2)	1% (0.0)
Human	0.083	105% (3.4)	97% (0.5)
	0.25	107% (8.6)	88% (2.8)
	0.5	94% (0.9)	82% (1.0)
	0.75	100% (10.9)	67% (2.6)
	1	106% (14.6)	53% (3.4)

Example 3: Thermodynamic and Kinetic Solubility

Compounds were assayed for aqueous solubility. Thermodynamic solubility was
 5 assayed using a shake-flask assay. Kinetic solubility was assayed using a filtration-based
 kinetic automated assay. In the kinetic solubility assay, the concentration was determined
 after 1 hour of shaking at 25°C. Results of the solubility assays are given in Table 4.

Table 4: Solubility

	pH	2	4.5	7.4
Compound 2	Thermodynamic Solubility (mg/mL)	0.143	0.21	0.177
	Kinetic Solubility (μM)	very low	162	184
Compound A	Thermodynamic Solubility (mg/mL)	57	64	50
	Kinetic Solubility (μM)	657	870	723

10 Example 4: Caco-2 Permeability Assay

Compounds were tested for monolayer transport properties using the MultiScreen
 Caco-2 Assay System (Millipore Corp., USA). Caco-2 cells were cultivated according to
 ATCC and Millipore recommendations in a humidified atmosphere at 37°C and 5% CO₂.
 Caco-2 cells were used to seed a 96 well filter plate at 12,000 cells per 0.11 cm² well and
 15 incubated for 21 days before the transport experiments. The integrity of cell monolayers
 was verified by measuring the transepithelial electrical resistance (TEER).

An assay solution of each tested compound was prepared from a DMSO stock
 solution at a final (working) concentrations of 1 μM. To determine drug transport in the
 apical to basolateral direction, 90 μL of the assay solutions were added to apical-side wells,
 20 and 250 μL of buffer was added to basolateral-side wells. To determine drug transport in
 the basolateral to apical direction, 250 μL of the assay solutions were added to basolateral-
 side wells, and 90 μL of buffer was added to the apical-side wells. The plates were

incubated at 37°C for 120 minutes, and samples were taken and analyzed by LC-MS/MS.

Apparent permeability (P_{app}) was calculated as follows:

$$P_{app} = \left(\frac{V_A}{Area * Time} \right) \times \left(\frac{AUC_A(t)}{AUC_D(0)} \right).$$

Efflux ratio was calculated as follows:

$$\frac{P_{app}(B \rightarrow A)}{P_{app}(A \rightarrow B)}$$

Recovery ratio was calculated as follows:

$$R(A \rightarrow B) = \frac{AUC_D(t) * V_D + AUC_A(t) * V_A}{AUC_D(0) * V_D}$$

The results of the permeability assay on Compound 2 are given in Table 5.

Table 5: Permeability Assay

	Compound 2	Compound A
$P_{app}(A-B)$, 10^{-6} cm/s	18	5.6
$P_{app}(B-A)$, 10^{-6} cm/s	14.4	5.7
Efflux Ratio	0.8	1.0
R(A-B), %	75	65
R(B-A), %	77	77

Example 5: HoPan Mouse Study

Compounds were assayed for *in vivo* efficacy in mouse models as follows.

14 days before treatment, a standard mouse diet was mixed with vitamin B5-deficient food, 1:1 for 7 days. 7 days before treatment and continuing throughout the study, mice were given vitamin B5-deficient food.

Cohort 1

In the first cohort, the effects of different doses of hopantenate (HoPan), a pan-PANK inhibitor, were assessed for the ability to cause mouse morbidity and mortality. HoPan was administered at doses of 50 (0.2), 100 (0.4), 200 (0.8) and 400 (1.6) mg(mmol)/kg/day, 6 mice/group. The weight of animals was monitored daily prior to dosing. Mortality or moribund condition requiring sacrifice of the animals was registered in the morning and in the evening each day. The study was terminated after 14 days of HoPan administration. During the study, mortality was observed in all treatment groups. Mortality was dose-and time-dependent, and is depicted in Figure 2. Body weight variation was also

dose- and time-dependent, and is depicted in Figure 3. The minimal dose of HoPan causing 100% mortality, 100 mg/kg/day, was chosen for the next step of the Study.

Cohort 2

- 5 Animals were dosed with 3 doses of vehicle or Compound 2 for 14 days in combination with HoPan at 100 mg/kg/day. Mortality or moribund condition requiring sacrifice of the animals were registered in the morning and in the evening each day. Survival results are shown in Figure 4. Body weight variability results are shown in Figure 5. Compound 2 effectively blocked the negative effects of treating animals with HoPan.
- 10 Survival of mice after administration of Compound 2 at 20 and 50 mg/kg was 90-100% at the conclusion of the study. The median survival of mice after Compound 2 administration at 10 mg/kg was approximately 14 days.

Incorporation by Reference

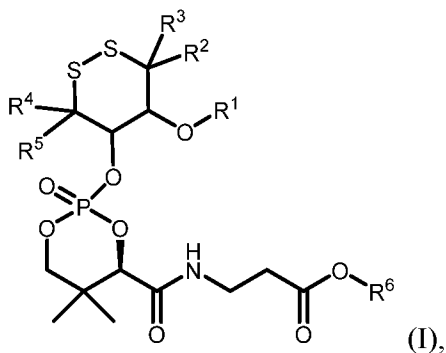
- 15 All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

20 Equivalents

- While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with
- 25 their full scope of equivalents, and the specification, along with such variations.

CLAIMS

1. A compound having the structure of formula (I) or a pharmaceutically acceptable salt or prodrug thereof:



5 wherein:

R^1 is alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^2 is H, alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

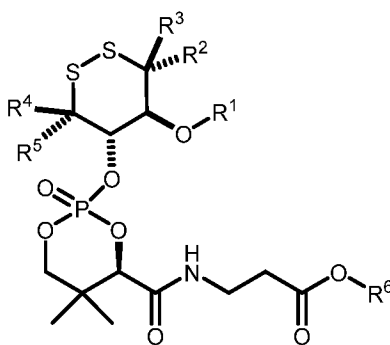
R^3 is H, alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

R^4 is H, alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl;

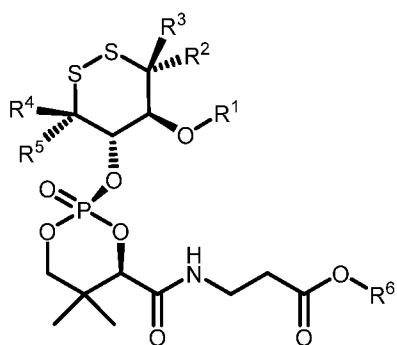
10 R^5 is H, alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl; and

R^6 is alkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl.

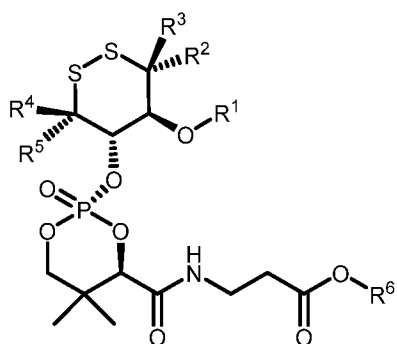
2. The compound of claim 1, wherein the compound is represented by the following structure:



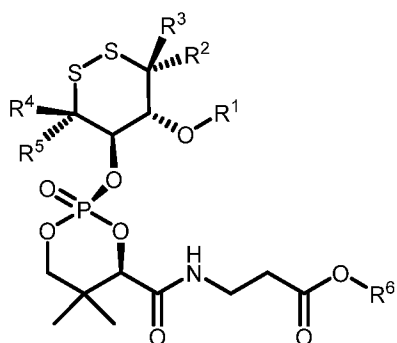
- 15 3. The compound of claim 1, wherein the compound is represented by the following structure:



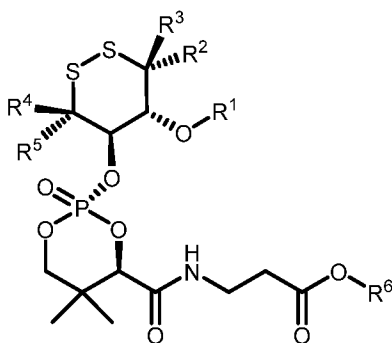
4. The compound of claim 1, wherein the compound is represented by the following structure:



5. The compound of claim 1, wherein the compound is represented by the following structure:



6. The compound of claim 1, wherein the compound is represented by the following structure:



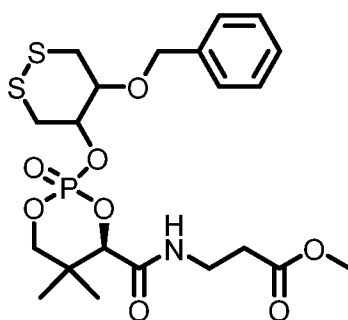
7. The compound of any one of claims 1 to 6, wherein:

R¹ is phenyl;

R², R³, R⁴, and R⁵ are H; and

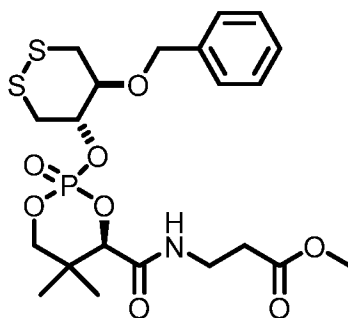
5 R⁶ is methyl.

8. The compound of claim 1, wherein the compound is represented by the following structure:



9. The compound of claim 1, wherein the compound is represented by the following structure:

10 structure:



10. A pharmaceutical composition comprising the compound of any one of claims 1-9.
11. A method of treating pantothenate-kinase-associated neurodegeneration, comprising administering a compound of any one of claims 1-9 or the pharmaceutical composition of claim 10.
- 5 12. A compound or composition according to any one of claims 1-10 for use in the treatment of pantothenate-kinase-associated neurodegeneration.

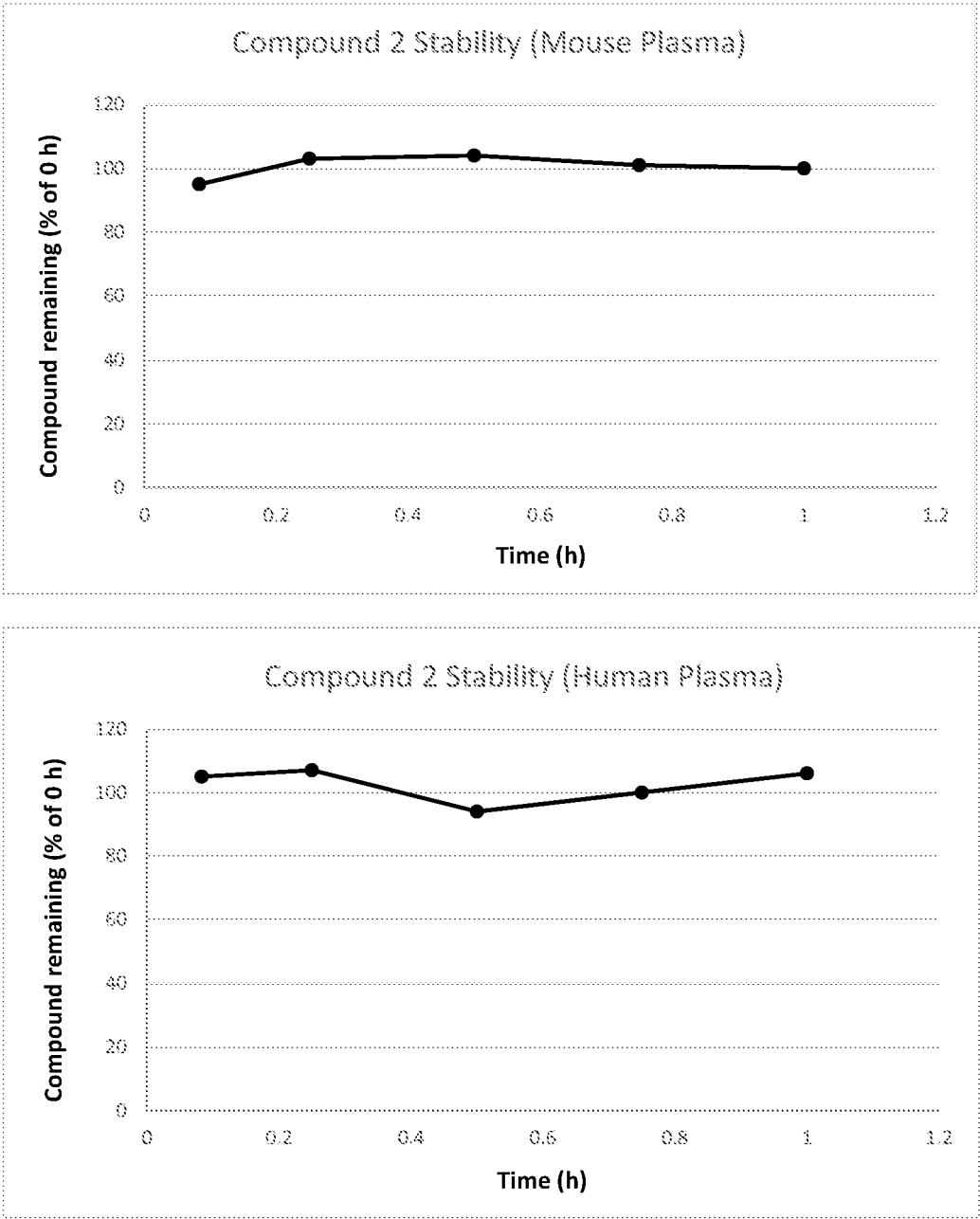


FIGURE 1

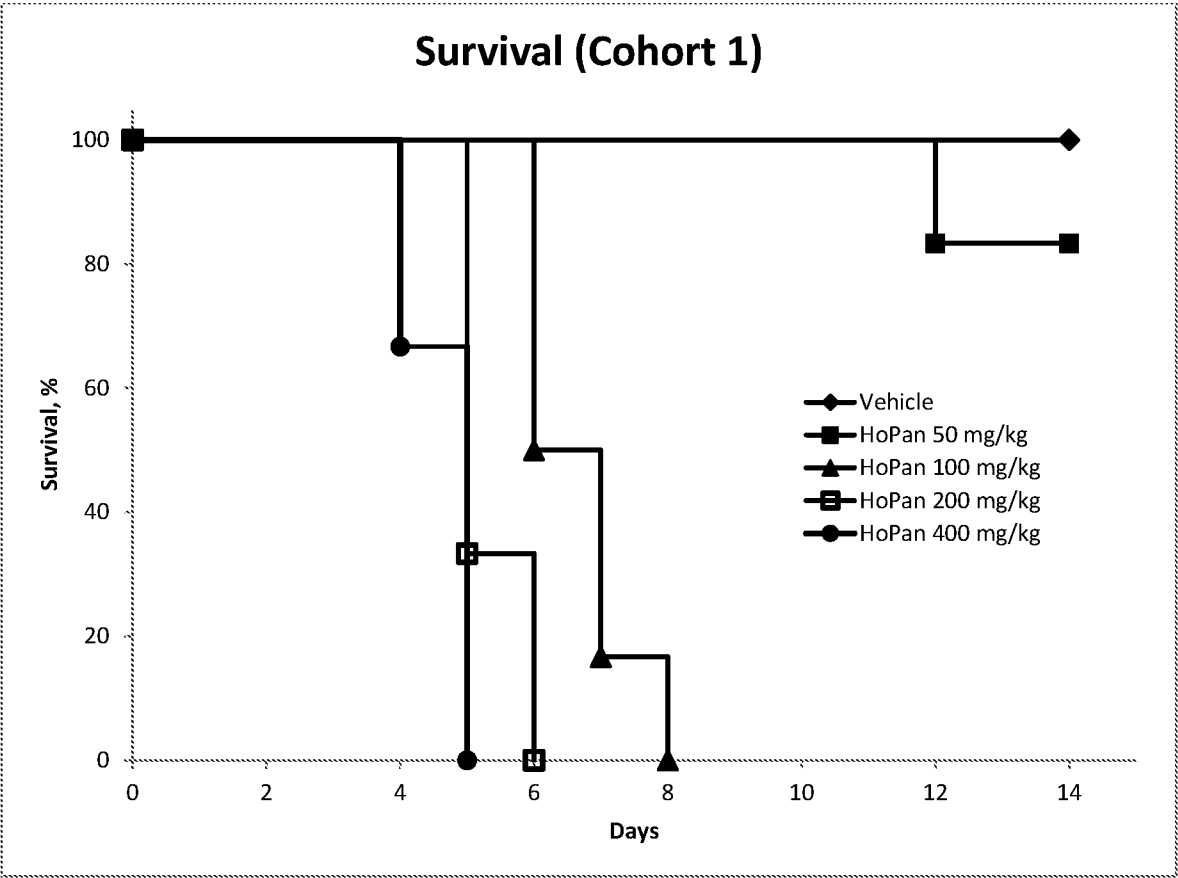


FIGURE 2

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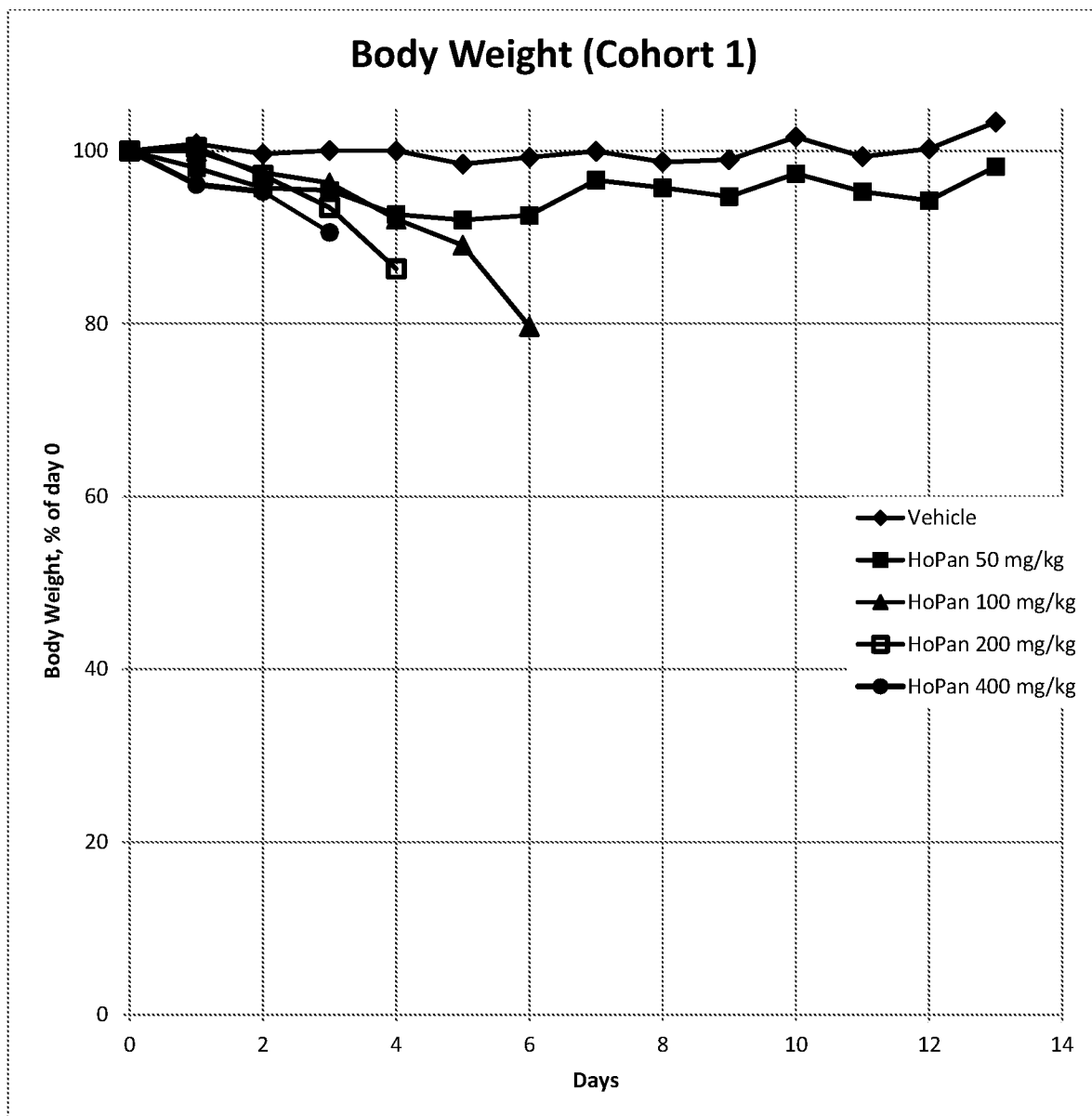


FIGURE 3

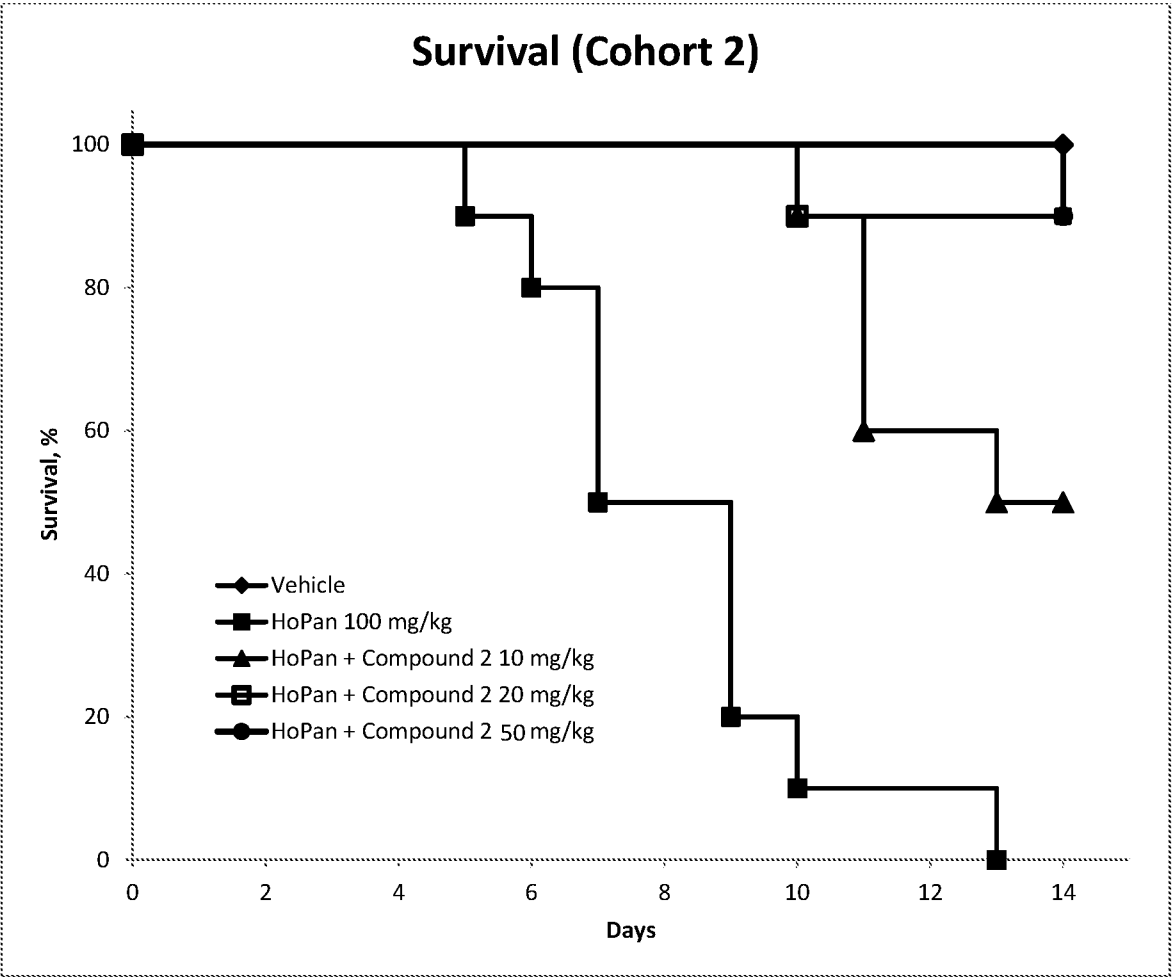


FIGURE 4

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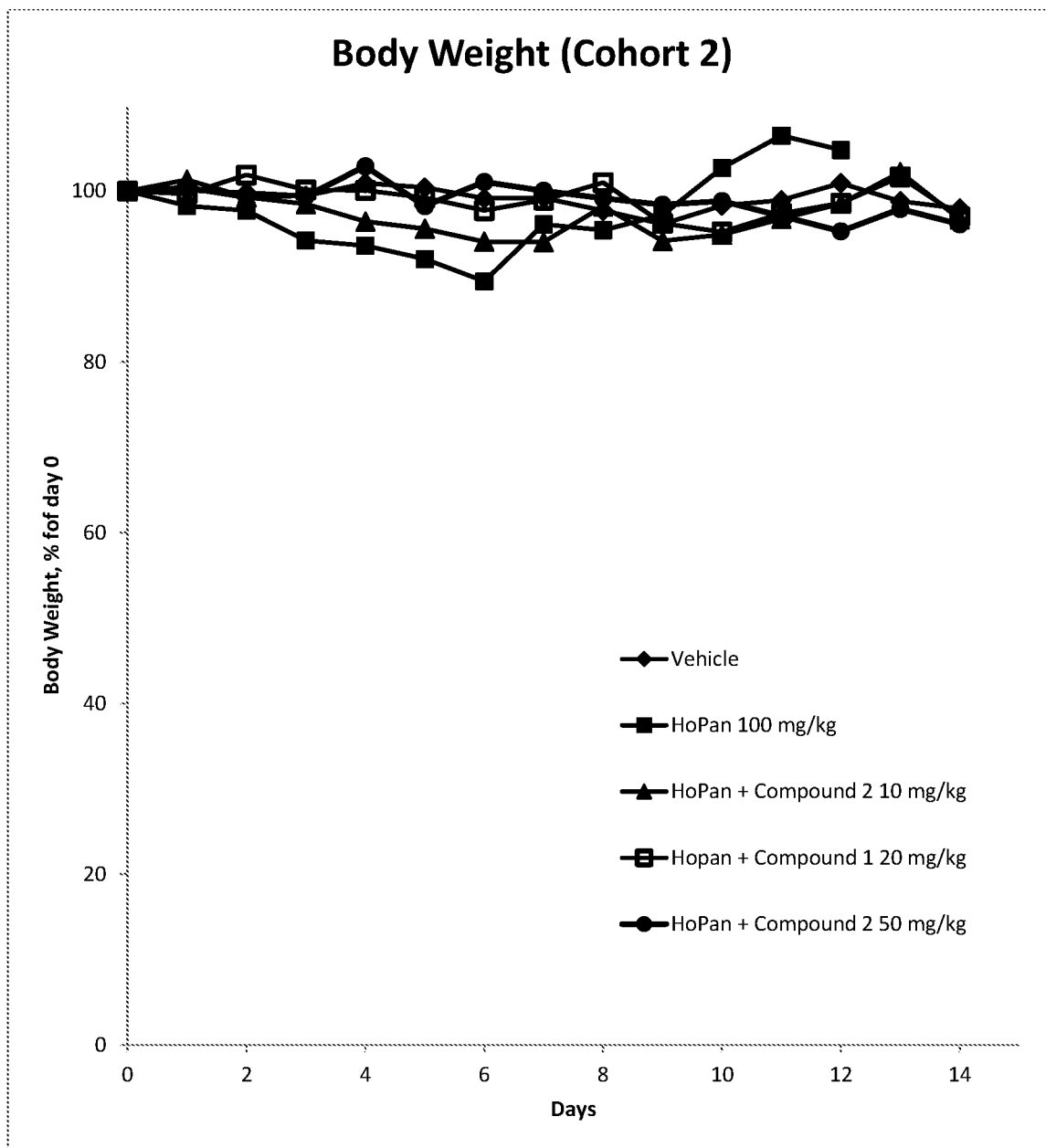


FIGURE 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 2017/013921

A. CLASSIFICATION OF SUBJECT MATTER		
C07F 9/6571 (2006.01) A61K 31/66 (2006.01) A61P 25/28 (2006.01)		
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)		
C07F 9/6571, 9/6574, 9/6584, 9/653, A61K 31/66, 31/683, A61P 25/28		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
STN, RUPAT, EAPO, Esp@senet, PAJ, USPTO, CIPO, DEPATIS, PCT Online, PATSEARCH		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7981874 B2 (MERCK SHARP & DOHME CORP.) 19.07.2011, abstract, claims	1-12
A	WO 2004/058778 A1 (J. URIACH Y COMPAÑIA S.A. et al.) 15.07.2004, claims	1-12
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* Special categories of cited documents: “A” document defining the general state of the art which is not considered to be of particular relevance “E” earlier document but published on or after the international filing date “L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) “O” document referring to an oral disclosure, use, exhibition or other means “P” document published prior to the international filing date but later than the priority date claimed “T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention “X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone “Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art “&” document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
30 March 2017 (30.03.2017)		11 May 2017 (11.05.2017)
Name and mailing address of the ISA/RU: Federal Institute of Industrial Property, Berezhkovskaya nab., 30-1, Moscow, G-59, GSP-3, Russia, 125993 Facsimile No: (8-495) 531-63-18, (8-499) 243-33-37		Authorized officer E.Guseva Telephone No. 495 531 65 15