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(54) **Title:** STABLE PANTETHEINE DERIVATIVES FOR THE TREATMENT OF PANTOTHENATE KINASE ASSOCIATED NEURODEGENERATION (PKAN) AND METHODS FOR THE SYNTHESIS OF SUCH COMPOUNDS

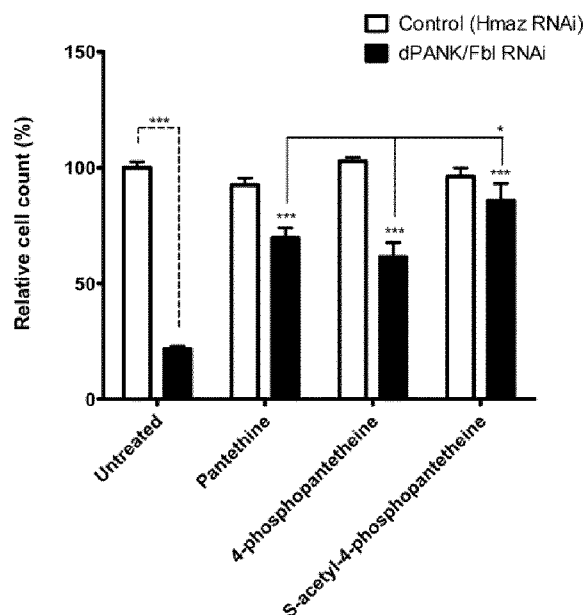


FIG. 3

(57) **Abstract:** The invention relates to (S)-acyl-4'-phosphopantetheine derivatives, methods of their synthesis, and related medical uses of such compounds. Preferred medical uses relate to the treatment of neurodegenerative diseases, such as PKAN.



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**STABLE PANTETHEINE DERIVATIVES FOR THE TREATMENT OF
PANTOTHENATE KINASE ASSOCIATED NEURODEGENERATION (PKAN)
AND METHODS FOR THE SYNTHESIS OF SUCH COMPOUNDS**

Field of the invention

The present invention relates to pantetheine derivatives, their synthesis and medical uses thereof.

Background of the invention

Pantothenate kinase-associated neurodegeneration (PKAN) is a rare genetic neurodegenerative disease. The disease is caused by mutations in the gene coding for pantothenate kinase 2 (PANK2). Pantothenate kinase 2 phosphorylates pantothenate to 4'-phosphopantothenate in the *de novo* biosynthesis pathway of coenzyme A. In PKAN patients, PANK2 (one of the four PANK isoforms known in humans and localized to the mitochondria) is affected and leads to severe neurodegeneration and premature death (Zhou, B. *et al.* Nat. Genet., 2001, 28, 345).

Pantothenate, 4'-phosphopantothenate, pantetheine and 4'-phosphopantetheine have all been suggested as potential agents for the treatment of PKAN. For example, 4'-phosphopantothenate and 4'-phosphopantetheine, both intermediates of the CoA metabolic pathway downstream of the pantothenate kinase step, were envisioned as potential treatment options for PKAN (Zhou, B. *et al.* Nat. Genet., 2001, 28, 345, WO 2003/008626). Pantethine (the disulfide of pantetheine) has been shown to rescue a *Drosophila* model of PKAN (Rana, A. *et al.*, PNAS, 2010, 107, 6988).

The use and testing of phosphorylated derivatives of pantothenate and pantetheine is hampered by a lack of suitable methods of preparation and purification procedures. Most research on the synthesis of various phosphorylated pantothenic acid derivatives has been done a long time ago, when the availability of analytical techniques was limited. Therefore, in many cases the structure and purity of products were just assumed, but not otherwise established. Moreover, in most cases the procedures are not well described and their reproducibility is questionable (King, T.E. *et al.* J. Biol. Chem., 1951, 191, 515; King, T.E. Science, 1950, 112, 562; J. Baddiley and E. M. Thain, J. Chem. Soc., 1953, 1610; Kopelevich, V. M., Khim. Farm. Zh., 1967, 11, 26; Hashimoto, Chem. Lett., 1972, 595).

Recently, a chemical synthesis of 4'-phosphopantothenate was described. The described synthesis method is a tedious 6-step synthesis procedure (Strauss *et al.*, Biochemistry, 2004, 43, 15520). In the same publication an older synthesis method for 4'-phosphopantetheine and 4'-phosphopantethenoyl cysteine is disclosed.

Although pantethine is a potent compound rescuing the *Drosophila* PKAN model, in serum pantethine is rapidly converted by pantetheinases to vitamin B5 and cysteamine (Wittwer *et al.*, J. Clin. Invest., 1985, 76, 1665) and therefore the compound pantethine is less likely to be an effective treatment for PKAN. This is confirmed by our own unpublished observations.

While a medical use of 4'-phosphopantetheine has already been speculated upon, a medical use of (S)-acyl-4'-phosphopantetheine derivatives has heretofore not been envisioned. In particular, it has not been suggested that such compounds could be useful in the treatment of neurodegenerative diseases, such as PKAN.

As a member of the group of (S)-acyl-4'-phosphopantetheine derivatives, (S)-acetyl-4'-phosphopantetheine has been structurally described (Lee, C-H. and Sarma, R.H., JACS, 1975, 97, 1225). However, an economically viable chemical synthesis method, or a possible medical use have not been reported for this compound.

(S)-benzoyl-4'-phosphopantetheine has been described as an intermediate in the synthesis of CoA derivatives (WO2012/17400). However, a pharmaceutical use of this compound was not envisaged.

Methods to increase the efficacy of compounds in medical treatment are known, in particular methods to increase the ability of pharmaceutical compounds to penetrate through membranes, or the blood-brain barrier. The medical use of phosphorylated compounds was often found to be limited by the compounds' poor ability to penetrate cell membranes. This has been attributed to the negative charge on the phosphate group which does not easily pass through cell membranes. Therefore, masking of the phosphate group, to yield a neutralized form, and to use the masked compound as a prodrug, allows the delivery of the medicament to the interior of the cells, where esterases present in the cells may subsequently cleave the protection groups from the phosphate groups, to release the active form of the drug. Thereby the bioavailability of biologically active phosphorylated compounds can be increased (Schultz, K. Bioorg. Med. Chem., 2003, 11, 885). Commonly used masking groups for this purpose are acyloxyalkyl groups, such as pivaloyloxymethyl (POM) and acetoxymethyl (AM). POM derivatives specifically have been shown to be stable in buffer and plasma.

Summary of the invention

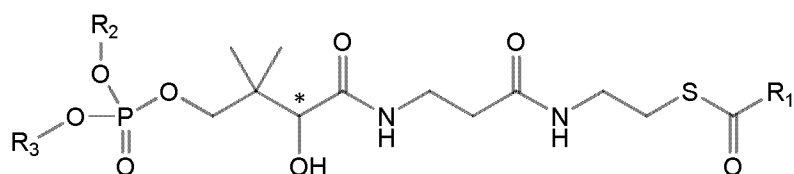
Against this background, it is an object of the invention to provide structurally novel compounds useful for treating neurodegenerative diseases, such as PKAN. It is another object of the invention to provide novel compounds useful for treating neurodegenerative diseases, such as PKAN, which compounds are more effective in treating the disease. It is another object of the invention to provide novel compounds useful for treating neurodegenerative diseases, such as PKAN, which compounds have less side effects, e.g., show decreased toxicity, when treating the disease. It is further an object of the invention to provide novel compounds useful for treating neurodegenerative diseases, which compounds are more stable in human serum.

It is another object of the invention to provide novel medical uses of compounds derived from intermediates of the coenzyme-A biosynthetic pathway. The present invention also relates to treatment methods using compounds of the invention, and to medicaments useful in treating neurodegenerative disorders, such as PKAN. The invention also relates to effective synthesis methods for compounds of the invention and compounds useful in treatment methods of the invention.

In one embodiment, the present invention relates to thioester derivatives of 4'-phosphopantetheine, such as (S)-acyl-4'-phosphopantetheines, *i.e.*, (S)-acyl-4'-phosphopantetheine derivatives, and their use for the treatment of neurodegenerative disorders, such as PKAN.

The present invention also relates to synthesis methods of (S)-acyl-4'-phosphopantetheines and diverse other derivatives of 4'-phosphopantetheine.

The present invention thus relates to a compound having the structural formula:

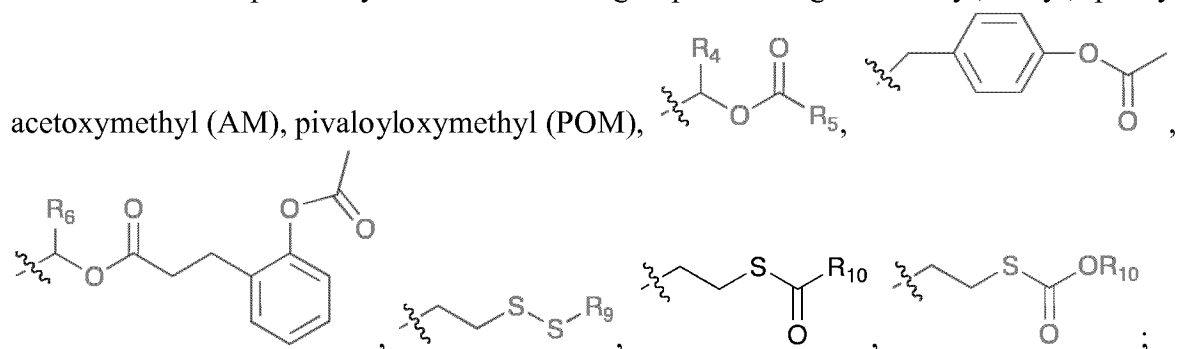


(Structure I),

wherein:

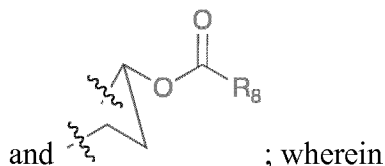
R₁ is -H, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₁₁, -C(O)OR₁₁, -C(O)NR₁₁R₁₂, -C=NR₁₁, -CN, -OR₁₁, -OC(O)R₁₁, -NR₁₁R₁₂, -NR₁₁C(O)R₁₂, -NO₂, -N=CR₁₁R₁₂ or -halogen; preferably C₁-C₁₀ alkyl, more preferably -methyl, -ethyl, -propyl or -butyl, such as *t*-butyl, most preferred -methyl;

R₂ and **R₃** are independently selected from the group consisting of: -methyl, -ethyl, -phenyl,



or

R_2 and R_3 jointly form a structure selected from the group consisting of:



R_4 is -H or -alkyl, preferably -methyl;

R_5 is -H or -alkyl, preferably C_1 - C_4 alkyl, most preferably -methyl or *t*-butyl;

5 R_6 is -H, -alkyl or $-CH_2(CO)OCH_3$;

R_7 is -H, -alkyl or -halogen;

R_8 is -H, -alkyl, preferably *t*-butyl;

R_9 is -H, -alkyl, preferably C_1 - C_4 alkyl;

R_{10} is -H, -alkyl, preferably C_1 - C_4 alkyl;

10 R_{11} and R_{12} are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy or halogen;

15 with the proviso that the compound is not (S)-acetyl-4'-phosphopantetheine or (S)-benzoyl-4'-phosphopantetheine;

or a pharmaceutically acceptable salt or solvate thereof.

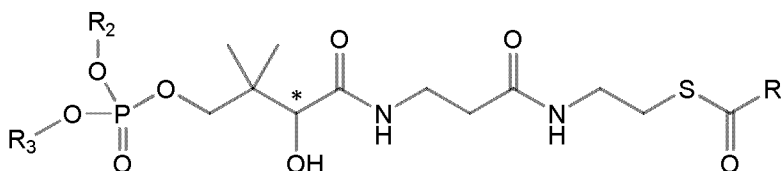
Preferred alkyl groups in the above definitions are -methyl, -ethyl, -propyl, -butyl, preferably *t*-butyl.

The D stereoisomer of Structure I is generally preferred.

20 In structures of the invention, a straight line overlayed by a wavy line denotes the covalent bond of the respective residue to the Structure I.

In preferred embodiments, R_2 and R_3 are identical residues. Bis-POM and bis-AM structures are particularly preferred.

Another aspect of the invention relates to a compound having the structural formula:



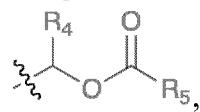
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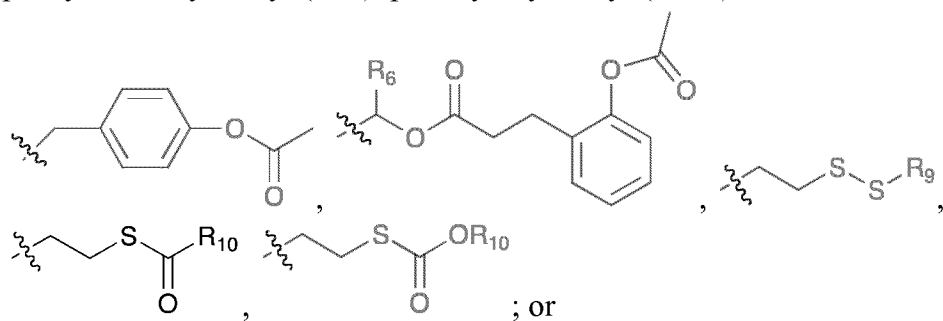
(Structure I),

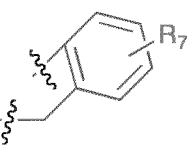
wherein:

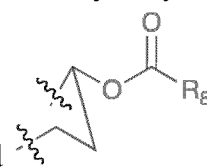
R₁ is -H, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₁₁, -C(O)OR₁₁, -C(O)NR₁₁R₁₂, -C=NR₁₁, -CN, -OR₁₁, -OC(O)R₁₁, -NR₁₁R₁₂, -NR₁₁C(O)R₁₂, -NO₂, -N=CR₁₁R₁₂ or -halogen; preferably C₁-C₁₀ alkyl, more preferably -methyl, -ethyl, -propyl or -butyl, such as *t*-butyl, most preferred is -methyl, most preferred -methyl;

R₂ and **R₃** are independently selected from the group consisting of: -H, -methyl, -ethyl, -

phenyl, acetoxymethyl (AM), pivaloyloxymethyl (POM), ,



R₂ and **R₃** jointly form a structure selected from the group consisting of: 

and ; wherein

R₄ is -H or -alkyl, preferably -methyl;

R₅ is -H or -alkyl, preferably C₁-C₄ alkyl, most preferably -methyl or *t*-butyl;

R₆ is -H, -alkyl or -CH₂(CO)OCH₃;

R₇ is -H or -alkyl or -halogen;

R₈ is -H or -alkyl, preferably *t*-butyl;

R₉ is -H, -alkyl, preferably C₁-C₄ alkyl;

R₁₀ is -H, -alkyl, preferably C₁-C₄ alkyl;

R₁₁ and **R₁₂** are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl,

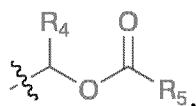
substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy or halogen;

or a pharmaceutically acceptable salt or solvate thereof;

for use as a medicament.

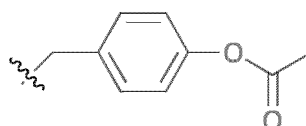
- 5 In particularly preferred embodiments of any aspect of the invention, R_2 and R_3 are both -ethyl or both -phenyl. In other preferred embodiments, R_2 is -ethyl and R_3 is -phenyl, or R_3 is -ethyl and R_2 is -phenyl.

In a second preferred embodiment, R_2 and R_3 are both



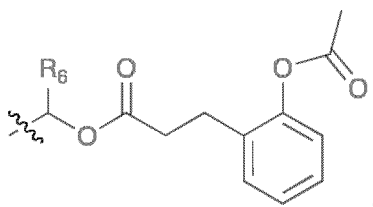
- 10 where R_4 is -H, methyl; R_5 is alkyl, such as methyl or t-butyl. Preferably R_4 is -H and R_5 is -methyl. Hence, R_2 and R_3 may both be acetoxymethyl (AM). In another embodiment R_4 is -H and R_5 is t-butyl. Hence, R_2 and R_3 may both be pivaloyloxymethyl (POM).

In a third preferred embodiment, R_2 and R_3 are both



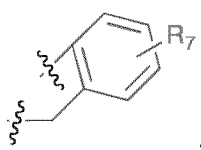
- 15 (acetooxybenzyl).

In a fourth preferred embodiment, R_2 and R_3 are both

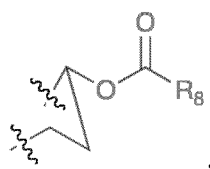


wherein R_6 is -H, -alkyl or $-\text{CH}_2(\text{CO})\text{OCH}_3$.

- 20 In a fifth preferred embodiment, the phosphate group forms a cyclic phosphate according to the following structure:

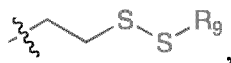


wherein R_7 is alkyl or halogen or the cyclic phosphate includes:



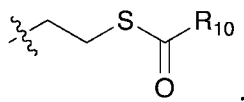
wherein R_8 is *t*-butyl.

In a sixth embodiment, R_2 and R_3 are both S-[(2-hydroxyethyl)sulfidyl]-2-thioethyl (DTE), or



5 wherein R_9 is alkyl, preferably -methyl, -ethyl, -propyl or -butyl, such as *t*-butyl.

In a seventh preferred embodiment, R_2 and R_3 are both S-acyl-2-thioethyl (SATE), or



wherein R_{10} is alkyl, preferably -methyl, -ethyl, -propyl or -butyl, such as *t*-butyl

Preferred alkyl groups are -methyl, -ethyl, -propyl, -butyl, preferably *t*-butyl.

10 The D stereoisomer of Structure I is generally preferred.

In preferred embodiments, said medicament is useful in the treatment of a neurodegenerative disease, epilepsy or cancer; preferably a neurodegenerative disease or epilepsy; even more preferred a neurodegenerative disease. In particularly preferred
15 neurodegeneration (PKAN).

Hence, an aspect of the invention relates to a method of treating a neurodegenerative disease, epilepsy or cancer (preferably a neurodegenerative disease or epilepsy; even more preferred a neurodegenerative disease) by administering to a subject in need a therapeutically effective amount of a compound according to the invention as described
20 hereinabove. In particularly preferred embodiments, the neurodegenerative disease is pantothenate kinase-associated neurodegeneration (PKAN).

The present invention also relates to a method of producing a compound of the invention as described hereinabove, said method comprising the step of reacting 4'-phosphopantothenate with an (S)-substituted mercaptoethylamine to yield (S)-
25 substituted-4'-phosphopantetheine.

In preferred embodiments the method includes enzymatic conversion of pantothenate to 4'-phosphopantothenate prior to the step of reacting 4'-phosphopantothenate with an (S)-substituted mercaptoethylamine (e.g., (S)-trityl-mercaptoethylamine) to yield (S)-substituted-4'-phosphopantetheine (e.g., (S)-trityl-4'-phosphopantetheine).

30 In preferred embodiments the method further comprises converting (S)-substituted-4'-phosphopantetheine (e.g., (S)-trityl-4'-phosphopantetheine) to 4'-phosphopantetheine.

In preferred embodiments the method further comprises converting 4'-phosphopantetheine by thioesterification to (S)-acyl-4'-phosphopantetheine (e.g., to (S)-acetyl-4'-phosphopantetheine).

In preferred embodiments the method further comprises formation of a phosphate ester of said (S)-acyl-4'-phosphopantetheine with a chloromethyl ester or a iodomethyl ester of a carboxylic acid.

5 The present invention also relates to a method of producing a compound of the invention as described hereinabove, said method comprising the steps of a) reacting pantothenate with an (S)-substituted mercaptoethylamine to yield (S)-substituted pantetheine, b) reacting the S-substituted pantetheine with a phosphorylating agent such as dibenzylchlorophosphate to obtain a phosphate ester of S-substituted 4'-phosphopantetheine such as S-trityl-4'-dibenzylphosphopantetheine and c) converting said
10 phosphate ester of (S)-substituted-4'-phosphopantetheine (e.g., (S)-trityl-4'-dibenzylphosphopantetheine) to 4'-phosphopantetheine.

The (S)-substituent can be any of the thiol protecting groups, known in the literature, usually resulting in thioether or thioester bond, e.g. trityl benzyl, benzoyl, stearoyl or palmitoyl group.

15 In preferred embodiments the method further comprises converting 4'-phosphopantetheine by thioesterification to (S)-acyl-4'-phosphopantetheine (e.g., to (S)-acetyl-4'-phosphopantetheine).

In preferred embodiments the method further comprises formation of a phosphate ester of said (S)-acyl-4'-phosphopantetheine with a chloromethyl ester or a iodomethyl ester of a
20 carboxylic acid.

In addition, the present invention relates to a method of producing a compound of the invention as described hereinabove, said method comprising the steps of reacting the (S)-substituted pantetheine such as (S)-acylpantetheine with a phosphorylating agent such as bis[(pivaloyloxy)methyl chlorophosphate to obtain a phosphate ester of S-substituted 4'-
25 phosphopantetheine such as bis(pivaloyloxymethyl) ester of S-acyl-4'-phosphopantetheine.

The (S)-substituent has a general formula $\mathbf{R}_1(\text{C}=\text{O})-$ wherein

\mathbf{R}_1 is -H, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or
30 unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₁₁, -C(O)OR₁₁, -C(O)NR₁₁R₁₂, -C=NR₁₁, -CN, -OR₁₁, -OC(O)R₁₁, -NR₁₁R₁₂, -NR₁₁C(O)R₁₂, -NO₂, -N=CR₁₁R₁₂ or -halogen; preferably C₁-C₁₀ alkyl, more preferably -methyl, -ethyl, -propyl or -butyl, such as *t*-butyl, most preferred is -methyl, most preferred -methyl.

35

Brief description of the figures

Figure 1 shows a chemoenzymatic route to (S)-acyl-4'-phosphopantetheine derivatives according to the invention. PANK = pantothenate kinase; R¹, R³, R⁴ are not necessarily the same as R₁, R₃, R₄ as defined in the claims.

- 5 Figure 2 shows improved stability of 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine in serum as compared to pantetheine (Example 2). PBS, phosphate buffered saline; FCS, fetal calf serum.

- Figure 3 shows that the rescue potential of 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine as compared to pantetheine in a PKAN cell model (Example 3). (S)-acetyl-4'-phosphopantetheine is most effective.

Figure 4 shows the rescue potential of pantetheine, 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine in cells treated with HOPAN (Example 4). (S)-acetyl-4'-phosphopantetheine is most effective.

- Figure 5 shows the rescue of 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine in Human PKAN cell model treated with HOPAN (Example 5). 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine are potent rescue molecules.

Figure 6 shows a comparison of cellular toxicity of pantetheine, 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine for human HEK293 cells (Example 6). Pantetheine is more toxic compared to 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine.

20 Detailed description of the invention

- The term “neurodegenerative disease”, in accordance with the present invention, shall be interpreted as having the meaning commonly understood in the art. In preferred embodiments, the “neurodegenerative disease” is selected from the group consisting of: Pantothenate kinase-associated neurodegeneration (PKAN), Alzheimer's disease,
- 25 Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS), Dementia Ataxia telangiectasia, Autosomal dominant cerebellar ataxia, Batten disease, Corticobasal degeneration, Creutzfeldt–Jakob disease, Fatal familial insomnia, Hereditary motor and sensory neuropathy with proximal dominance, Infantile Refsum disease, JUNQ and IPOD, Locomotor ataxia, Lyme disease, Machado–Joseph disease, Mental retardation and
- 30 microcephaly with pontine and cerebellar hypoplasia, Multiple system atrophy, Neuroacanthocytosis, Niemann–Pick disease, Pontocerebellar hypoplasia, Refsum disease, Sandhoff diseases, Shy-Drager syndrome, Spinocerebellar ataxia, Subacute combined degeneration of spinal cord, Subacute sclerosing panencephalitis, Tabes dorsalis, Tay–Sachs disease, Toxic encephalopathy, and Wobbly hedgehog syndrome. Preferred
- 35 neurodegenerative disorders, in the context of the present invention are Pantothenate kinase-associated neurodegeneration (PKAN), Alzheimer's disease, Parkinson's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS), Dementia; most preferably Pantothenate kinase-associated neurodegeneration (PKAN).

Within the context of the present invention, "alkyl" refers to a straight or branched hydrocarbon chain radical consisting of carbon and hydrogen atoms, containing no saturation, having one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, n-pentyl, etc. Alkyl radicals may be optionally substituted by one or more substituents such as a aryl, halo, hydroxy, alkoxy, carboxy, cyano, carbonyl, acyl, alkoxycarbonyl, amino, nitro, mercapto, alkylthio, etc. If substituted by aryl we have an "Aralkyl" radical, such as benzyl and phenethyl.

"Alkenyl" refers to an alkyl radical having at least two carbon atoms covalently connected by a double bond.

"Cycloalkyl" refers to a stable 3- to 10-membered monocyclic or bicyclic radical which is saturated or partially saturated, and which consist solely of carbon and hydrogen atoms, such as cyclohexyl or adamantyl. Unless otherwise defined, the term "cycloalkyl" is meant to include cycloalkyl radicals which are optionally substituted by one or more substituents such as alkyl, halo, hydroxy, amino, cyano, nitro, alkoxy, carboxy, alkoxycarbonyl.

"Aryl" refers to single and multiple ring radicals, including multiple ring radicals that contain separate and/or fused aryl groups. Typical aryl groups contain from 1 to 3 separated or fused rings and from 6 to about 18 carbon ring atoms, such as phenyl, naphthyl, indenyl, fenanthryl or anthracyl radical. The aryl radical may be optionally substituted by one or more substituents such as hydroxy, mercapto, halo, alkyl, phenyl, alkoxy, haloalkyl, nitro, cyano, dialkylamino, aminoalkyl, acyl, alkoxycarbonyl, etc.

"Heterocyclyl" refers to a stable 3-to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, preferably a 4-to 8-membered ring with one or more heteroatoms, more preferably a 5-or 6-membered ring with one or more heteroatoms. It may be aromatic or not. For the purposes of this invention, the heterocycle may be a monocyclic, bicyclic or tricyclic ring system, which may include fused ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidised; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated or aromatic. Examples of such heterocycles include, but are not limited to, azepines, benzimidazole, benzothiazole, furan, isothiazole, imidazole, indole, piperidine, piperazine, purine, quinoline, thiadiazole, tetrahydrofuran, coumarine, morpholine; pyrrole, pyrazole, oxazole, isoxazole, triazole, imidazole, etc.

"Alkoxy" refers to a radical of the formula -ORa where Ra is an alkyl radical as defined above, e. g., methoxy, ethoxy, propoxy, etc.

References herein to "substituted" groups in the compounds of the present invention refer to the specified moiety that is substituted at one or more available positions by one or more suitable groups, e. g., halogen such as fluoro, chloro, bromo and iodo, cyano, hydroxyl, nitro, azido, alkanoyl such as a C1-6 alkanoyl group such as acyl and the like, carboxamido, alkyl groups including those groups having 1 to about 12 carbon atoms or from 1 to about

6 carbon atoms and more preferably 1-3 carbon atoms, alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms, alkoxy groups having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms, aryloxy such as phenoxy, alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms, alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms, alkylsulfonyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms, aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl or naphthyl and aralkyl such as benzyl. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

The term "pharmaceutically acceptable salts or solvates" refers to any pharmaceutically acceptable salt, solvate, or any other compound which, upon administration to the recipient is capable of providing (directly or indirectly) a compound as described herein. However, it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the invention since those may be useful in the preparation of pharmaceutically acceptable salts. The preparation of salts, prodrugs and derivatives can be carried out by methods known in the art. For instance, pharmaceutically acceptable salts of compounds provided herein are synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts are, for example, prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent or in a mixture of the two. Generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. Examples of the acid addition salts include mineral acid addition salts such as, for example, hydrochloride, hydrobromide, hydroiodide, sulphate, nitrate, phosphate, and organic acid addition salts such as, for example, acetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, methanesulphonate and p-toluenesulphonate. Examples of the alkali addition salts include inorganic salts such as, for example, sodium, potassium, calcium, ammonium, magnesium, aluminium and lithium salts, and organic alkali salts such as, for example, ethylenediamine, ethanolamine, N,N-dialkylmethanolamine, triethanolamine, glucamine and basic aminoacids salts.

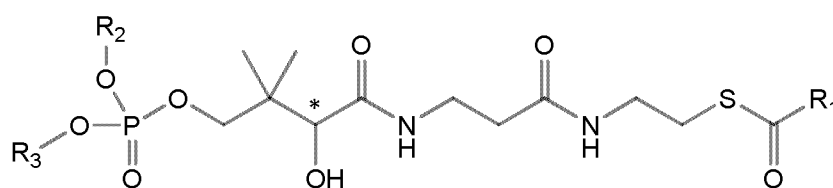
The present invention generally relates to the treatment of neurodegenerative diseases and compounds useful in such treatment. In a preferred embodiment, the neurodegenerative disease is pantothenate kinase-associated neurodegeneration (PKAN).

PKAN is believed to be caused by impaired function of the enzyme pantothenate kinase 2. Pantothenate kinase is required for the synthesis of Coenzyme A (Rana, A. *et al.*, PNAS, 2010, 107, 6988). It has been demonstrated in a fly model for PKAN, that the compound pantethine restores levels of Coenzyme A and thereby rescues all disease characteristics of PKAN (Rana, A. *et al.*, PNAS, 2010, 107, 6988). However, the use of pantethine to treat

human subjects with pantethine is limited by the fact that pantethine is not stable in human serum and in human intestines and is rapidly converted into vitamin B5 and cysteamine (Wittwer et al., J Clin Invest, 1985, 76, 1665) and pantethine is toxic to wild type flies (Rana, A. *et al.*, PNAS, 2010, 107, 6988). The present invention overcomes this deficiency by providing treatment methods based on compounds which have improved stability in serum and which compounds are less toxic than pantethine.

In a first aspect, the present invention relates to a novel class of pharmaceuticals, for use in the treatment of neurodegenerative diseases (preferably PKAN), herein denoted as (S)-acyl-4'-phosphopantetheines. From this group of compounds only (S)-acetyl-4'-phosphopantetheine (Lee, C-H. and Sarma, R.H., JACS, 1975, 97, 1225) and (S)-benzoyl-4'-phosphopantetheine (WO 2012/017400) were structurally known. The pharmaceutical potential of this group of compounds (in particular of the known substances (S)-acetyl-4'-phosphopantetheine and (S)-benzoyl-4'-phosphopantetheine) has not been realized before the present invention.

In a second aspect, the invention relates to prodrugs that liberate biologically active (S)-acyl-4'-phosphopantetheines in mammalian cells. In these prodrugs the phosphate group is masked by moieties that facilitate the transfer of these compounds through cell membranes as well as the blood-brain-barrier. Such prodrugs have the following chemical structure:



(Structure I),

in which R₁ is as defined in the appended claims, or R₁ may be -CH₃, -C₂H₅, -C₃H₇, -C₄H₉; and R₂ and R₃ are as defined in the appended claims, or R₂ and R₃ may be -CH₂O(CO)tBu, -CH₂O(CO)Me. The D-isomer is preferred.

Phosphate ester compounds are preferred due to their increased potential to penetrate membranes or, *e.g.*, the blood-brain barrier. Suitable methods of producing such phosphate esters of S-acyl-phosphopantetheine are well known in the art. An exemplary synthetic method is provided in Example 7. A review of other suitable methods for forming prodrugs by esterification of phosphate groups of pharmaceutically active ingredients is provided by Schultz (2003, "Prodrugs of biologically active phosphate esters", Bioorg Med Chem 11: 885), specific reference to which is hereby made, and the contents of which is incorporated herein by reference to the extent permitted.

A third aspect of the invention relates to a novel and economically viable methods for the production of (S)-acyl-4'-phosphopantetheine derivatives, as defined in the claims, including their prodrugs having a masked phosphate group. Masking of a phosphate group is preferably esterification of the phosphate group.

The present invention is based on the observation that two novel pantethine-derivatives, namely 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine exhibit increased stability in human serum and are less toxic when compared to pantethine. In addition, it was surprisingly found that (S)-acetyl-4'-phosphopantetheine is more effective than pantethine (and 4'-phosphopantetheine) in a drosophila disease model for PKAN.

Based on the efficient rescue of cells in neural disease models by 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine, the increased stability of the two compounds in serum and on the reduced toxicity of the compounds, we conclude that the group of compounds falling under the generic Structure I, as defined in the claims, is superior to all presently known PKAN therapeutics, proposed PKAN therapeutics, and/or PKAN therapeutics in development. *N.b.*, currently there are no approved therapeutics available to halt or reverse the symptoms of PKAN. Compounds of the generic Structure I are useful therapeutics for neurodegenerative disorders of the invention, in particular for PKAN.

It is known that in fly and cell models of PKAN, the levels of protein acetylation are decreased (Siudeja et al., EMBO Mol Med 2011, 3, 755). We have shown that histone deacetylase (HDAC) inhibitors, such as Trichostatin A (TSA) and valproic acid rescue the protein acetylation defect in PKAN models. Pantethine also rescues the acetylation defects in PKAN models. The source for the acetyl group required for protein acetylation is acetyl-coenzyme A. The inventors believe that (S)-acetyl-4'-phosphopantetheine is a compound that is rapidly converted into acetyl-CoA, thereby increasing protein acetylation. For a variety of diseases HDAC inhibitors are being used and specifically the valproic acid is currently used in diseases ranging from cancer, to epilepsy, to neurodegeneration. The disadvantage is that valproic acid has severe side effects. We believe that (S)-acetyl-4'-phosphopantetheine and its derivatives according to the invention can serve as an alternative for valproic acid in restoring or increasing protein acetylation without causing severe side effects. Compounds of Structure I, such as (S)-acetyl-4'-phosphopantetheine can serve as an alternative to valproic acid in various therapies. Therefore, (S)-acetyl-4'-phosphopantetheine derivatives, such as (S)-acetyl-4'-phosphopantetheine derivatives, can be used in therapy for diseases in which valproic acid is currently used. Specific examples are: cancer, epilepsy, Alzheimer's disease.

Hence, particularly preferred medical indications, in the context of the invention, are neurodegenerative diseases as defined above, in particular PKAN, but also epilepsy, and cancer.

The surprising finding that compounds of the invention show superior stability over, *e.g.*, pantethine in serum may be explained *ex post* by their lower sensitivity to pantetheinases. The increased rescue potential of (S)-acylated compounds of the invention, such as (S)-acetyl-4'-phosphopantetheine over 4'-phosphopantetheine is currently not well understood, because one would expect that both molecules could equally well be converted into Coenzyme A, which is the molecule which is lacking in PKAN and most likely causing the disease. Our results show that the compounds of the invention, such as (S)-acetyl-4'-phosphopantetheine and its derivatives, have a higher rescue potential, suggesting that it is

more efficiently converted into Coenzyme A, or converted directly into acetyl-CoA and this maybe beneficial. This, however, is merely speculation. The reason for the observed superior potency of the compounds of the invention in the treatment of the above mentioned diseases is really not well understood.

5 In the scope of this invention, we have synthesized 4'-phosphopantothenate, 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine and tested its ability to rescue cells in cell line models of PKAN. We demonstrated that (S)-acetyl-4'-phosphopantetheine is superior to the previously proposed 4'-phosphopantetheine (having a free sulfhydryl group), phosphopantothenate and pantethine in restoring normal growth of a PKAN cell
10 model with impaired pantothenate kinase activity.

We have also determined that (S)-acyl-4'-phosphopantetheine and its derivatives, such as (S)-acetyl-4'-phosphopantetheine, are more stable in serum than pantethine with free sulfhydryl group.

15 In preferred embodiments, derivatization of the phosphate group of (S)-acyl-4'-phosphopantetheines with acyloxyalkyl groups, such as pivaloyloxymethyl (POM) and acetoxymethyl (AM) provides further advantageous properties, because such prodrug derivatives penetrate the blood-brain-barrier of mammals more easily. This is specifically important for the effective treatment of neurodegenerative diseases.

20 The derivatization of the phosphate group is chemically easily achieved when using (S)-acyl-4'-phosphopantetheines while, in contrast, such derivatization is much more difficult, if not impossible, to achieve in the case of 4'-phosphopantetheine. This is due to the interference of the free sulfhydryl group in the required chemical reactions.

The design a viable synthetic route from the commercially available pantothenate (vitamin B5) to (S)-acyl-4'-phosphopantetheines forms an important aspect of the present invention.
25 Only through the availability of this synthesis route it became possible to determine the improved biological activity of the latter compounds.

Briefly, pantothenic acid is enzymatically converted to 4'-phosphopantothenate. Isolated 4'-phosphopantothenic acid is then reacted with (S)-substituted mercaptoethylamines in the presence of a coupling reagent and an activator in a solvent. (S)-trityl-4'-
30 phosphopantetheine obtained this way is isolated from the reaction mixture followed by its conversion to 4'-phosphopantetheine. Finally, 4'-phosphopantetheine is converted to (S)-acyl-4'-phosphopantetheine by thioesterification with the corresponding thioacid, such as thioacetic acid.

Alternatively, pantothenic acid is reacted with previously prepared (S)-substituted
35 mercaptoethylamines in the presence of a coupling reagent and an activator in a solvent. (S)-trityl-4'-pantetheine obtained this way is isolated from the reaction mixture, followed by its phosphorylation with dibenzylchlorophosphate in the presence of a base in a solvent. Removing of benzyl and trityl protecting group gives 4'-phosphopantetheine. Finally, 4'-phosphopantetheine is converted to (S)-acyl-4'-phosphopantetheine by thioesterification
40 with the corresponding thioacid, such as thioacetic acid.

Masking the phosphate group includes the formation of phosphate esters from (S)-acyl-4'-phosphopantetheine with the corresponding chloro-methylester of the carboxylic acid, such as chloromethyl pivalate and chloromethyl acetate.

5 Alternatively, masking of the phosphate group can be done by phosphorylating S-substituted pantetheine such as (S)-acetyl-4'-pantetheine with a suitable phosphorylating agent such as bis[(pivaloyloxy)methyl chlorophosphate in the presence of a base in a solvent to obtain bis(pivaloyloxymethyl) ester of S-acyl-4'-phosphopantetheine

10 The present invention further provides pharmaceutical compositions comprising a compound of invention, or a pharmaceutically acceptable salt thereof, preferably together with a pharmaceutically acceptable carrier, adjuvant, or vehicle, for administration to a patient.

Examples of pharmaceutical compositions of the invention include any solid (tablets, pills, capsules, granules etc.) or liquid (solutions, suspensions or emulsions) composition for oral, topical, parenteral or sublingual administration.

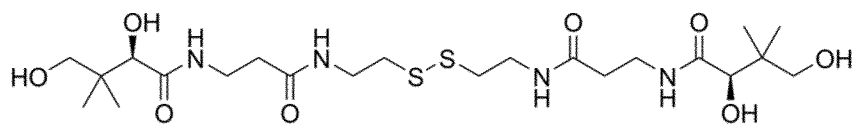
15 In a preferred embodiment the pharmaceutical compositions are in oral form, either solid or liquid. Suitable dose forms for oral administration (including sublingual administration) may be tablets, capsules, syrups or solutions and may contain conventional excipients known in the art such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize starch, 20 calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable wetting agents such as sodium lauryl sulfate.

25 Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, and intraperitoneal, intramuscular, sub-cutaneous, sublingual, topical and intravenous administration. Oral administration (in particular sublingual administration) is preferred because of the convenience for the patient and the chronic character of the diseases to be treated.

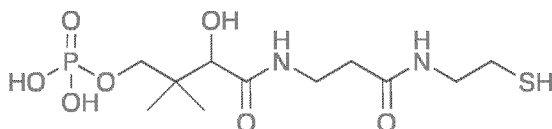
30 The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or at different time.

35 A suitable dose for compounds of the invention is from 0.1 to 1000 mg/kg body weight/day, preferably 0.1 to 100 mg/kg body weight/day, more preferably 1 to 50 mg/kg body weight/day. Administration is preferably 1x, 2x, 3x, or 4x per day, preferably 1x or 2x per day.

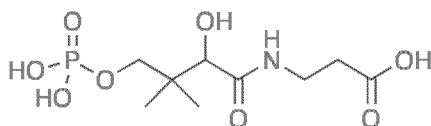
The following structural formulae are relevant in the context of the present invention:



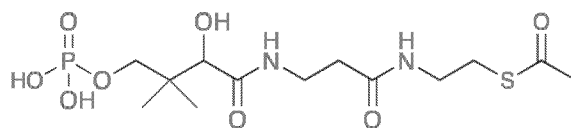
(pantethine);



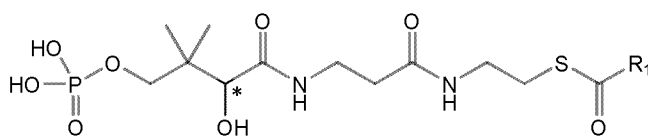
(4'-phosphopantetheine);



(4'-phosphopantothenate);



((S)-acetyl-4'-phosphopantetheine);



((S)-acyl-4'-phosphopantetheines).

Examples

Example 1: Synthesis of (S)-acyl-4'-phosphopantetheines

Pantothenic acid was enzymatically converted to 4'-phosphopantothenate. Isolated 4'-phosphopantothenic acid was then reacted with (S)-substituted mercaptoethylamines in the presence of a coupling reagent and an activator in a solvent. (S)-trityl-4'-phosphopantetheine obtained this way was isolated from the reaction mixture, followed by its conversion to 4'-phosphopantetheine. Finally, 4'-phosphopantetheine was converted to (S)-acyl-4'-phosphopantetheine by thioesterification with the corresponding thioacid, such as thioacetic acid. In one example, the phosphate group was masked by esterification, to improve the membrane penetration potential of the compound. Masking the phosphate group was effected by the formation of phosphate esters from (S)-acyl-4'-phosphopantetheine with the corresponding halomethyl ester of the carboxylic acid, such as chloromethyl pivalate, iodomethyl pivalate, chloromethyl acetate and iodomethyl acetate.

Example 2: Increased stability of 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine in serum as compared to pantethine.

This example shows the superior stability of (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine in fetal calf serum (FCS) in comparison to pantetheine.

Pantetheine has been shown to be rapidly converted in serum by pantetheinases to vitamin B5 and cysteamine (Wittwer et al., 1985, 76, 1665). We synthesized (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine as described in Example 1 and subsequently evaluated the stability of these compounds in FCS.

Materials and Methods: Pantetheine (purchased from Sigma), (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine were incubated at a final concentration of 1 mM in FCS and in PBS for 30 minutes at 37°C. After incubation, the samples were processed to remove proteins and HPLC analysis was used to assess the amount of remaining compound indicating the stability of the respective compounds.

Results: Pantetheine is significantly degraded (60%), most likely by pantetheinase, whereas (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine are stable and degrade by less than 10%. The Experiment was performed in triplicate, error bars indicate standard deviation in Figure 2.

Example 3: Rescue potential of 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine in cellular PKAN disease model

The down-regulation of dPANK/fbl (PANK ortholog in Drosophila) using RNAi approach in Drosophila S2 cells is an established in-vitro PKAN disease model (Rana, A. et al., PNAS, 2010, 107, 6988; Siudja et al., EMBO Mol med. 2011, 3, 755; Siudeja et al., PLoS One 2012, 7, e443145). Down-regulation of dPANK/fbl by RNAi, causes a decrease in the survival of cells. A rescuing compound such as pantetheine, 4'-phosphopantetheine or (S)-acetyl-4'-phosphopantetheine restores the cell survival. The following example is included to compare the rescue efficiency of pantetheine, (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine in such model system.

Materials and Methods: Drosophila Schneider's S2 cells were cultured and subjected to RNAi treatment as described previously (Rana, A. et al., 2010, 107, 6988.). 100 µM of pantetheine, (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine was added to the cells and the rescue potential was assessed by determining the cell survival.

Result: The result is shown in Figure 3. The Figure indicates that both (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine rescued the cell count defect significantly in dPANK/fbl down-regulated Drosophila-S2 cells. (S)-acetyl-4'-phosphopantetheine is surprisingly found to have superior rescue potential as compared to pantetheine and 4'-phosphopantetheine. Experiment was performed in triplicate, error bars indicate standard deviation.

Example 4: Rescue potential in HOPAN assay

In an additional experiment, Drosophila-S2 cells treated with the chemical inhibitor HOPAN (hopanthenate, CAS 17097-76-6, IUPAC: calcium 4-[(2R)-2,4-dihydroxy-3,3-dimethylbutanoyl]amino]butanoate). Cells treated with HOPAN also serve as a model for

PKAN. Cells treated with HOPAN also show a reduction in cell viability. Herewith, the result is included to compare the rescue efficiency of pantethine, (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine in such model system.

Materials and Methods: *Drosophila* Schneider's S2 cells were cultured and subjected to HOPAN (0.5mM) treatment with and without (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine for two days (Siudeja.K. et al., EMBO Mol Med. 2011, 3, 755). 100 μ M of (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine was compared for its rescue efficiency.

Result: The result as shown below indicates (S)-acetyl-4'-phosphopantetheine significantly rescued the HOPAN (0.5mM) induced cell count defect compared to 4'-phosphopantetheine. Experiment was performed in triplicate; error bars indicate standard deviation in Figure 4.

Example 5: Rescue of HEK cells in HOPAN model

Similar to *Drosophila*-S2 cells, the PKAN disease model can also be induced using HOPAN in mammalian cell lines. Rescue efficiency of (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine was studied in HOPAN induced PKAN model system, namely in mammalian HEK293 cells.

Materials and Methods: HEK293 cells were cultured in vitamin B5 deficient DMEM (Thermo Scientific) supplemented with 10% dialysed FCS (Thermo Scientific) with and without HOPAN (0.5mM) and (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine for 4 days. 100 μ M of (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine was compared for its rescue efficiency.

Result: The result as shown below indicates (S)-acetyl-4'-phosphopantetheine and 4'-phosphopantetheine significantly reduced the HOPAN induced cell count defect also in mammalian-HEK293 cell system. Experiment was performed in triplicate; error bars indicate standard deviation in Figure 5.

Example 6: Toxicity

Human HEK293 cells were treated with increasing concentrations of pantethine, 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine to determine and compare the toxicity of the compounds. A drop in cell counts indicates toxicity. Pantethine is inducing toxicity at lower concentrations compared to 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine, demonstrating that 4'-phosphopantetheine and (S)-acetyl-4'-phosphopantetheine are less toxic compared to pantethine. See Figure 6.

Example 7: Preparation of bis(pivaloyloxymethyl) ester of S-acyl-4'-phosphopantetheine

A phosphate-ester derivative according to the invention may be synthesized using the following procedure:

Iodomethyl pivalate is freshly prepared by reaction of chloromethyl pivalate (0.151 g, 1 mmol) with sodium iodide (0.3 g, 2 mmol) in acetonitrile (1 mL) at 30°C for 5 h under N₂ atmosphere. To the reaction mixture is added dichloromethane (5 mL) and water (5 mL) and stirred. After phase separation the organic layer is washed with 2% aq. sodium thiosulfate (Na₂S₂O₃) and concentrated under vacuum to give iodomethyl pivalate as a yellowish oil 0.194 g (0.8 mmol, 80 %). S-acetyl-4'-phosphopantetheine (0.04 g, 0.1 mmol) is suspended in DMF (1 mL). Triethylamine (0.042 mL, 0.3 mmol) and iodomethylpivalate (0.073 g, 0.3 mmol) are added. The mixture is stirred at around 40°C overnight, then the solvent is removed and the residue dissolved in ethyl acetate. The mixture is washed with brine, dried over sodium sulfate, filtrated and concentrated under reduced pressure. Purification of the crude product is followed by column chromatography to give 0.016 g of bis(pivaloyloxymethyl) ester of S-acetyl-4'-phosphopantetheine (0.025 mmol, 25 %).

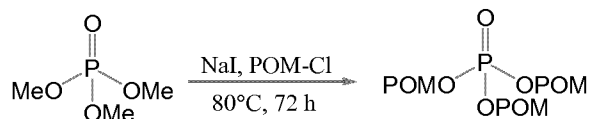
Phosphate-ester derivatives of the invention have improved bio-availability, due to their increased membrane permeation potential.

Example 8: Alternative method for Preparation of bis(pivaloyloxymethyl) ester of S-acetyl-4'-phosphopantetheine

Preparation of phosphorylating reagent

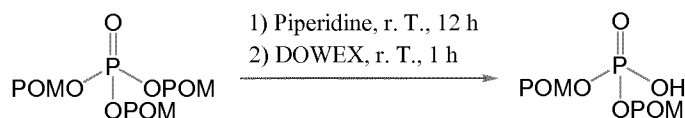
Bis(POM) chloro phosphate for the phosphorylation of S-acetyl-pantetheine was prepared according to the published literature (Hwang Y et al., Organic Letters. 2004, 6, 1555; Ruda, GF et al., ChemMedChem. 2007, 2, 1169):

Preparation of Tris(POM) phosphate



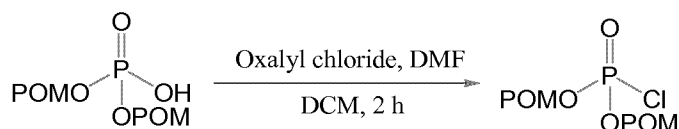
To a solution of trimethyl phosphate (7.01 g, 50 mmol) in dry CH₃CN (42 mL) were sequentially added chloromethylpivalate (29.35 g, 195 mmol) and NaI (22.52 g, 150 mmol). The reaction mixture was heated at reflux (80 °C) for 72 hours, cooled to ambient temperature and diluted with Et₂O (400 mL). The organic phase was washed with water (2 x 100 ml), saturated Na₂S₂O₃ solution (2 x 100 mL), dried over Na₂SO₄ and concentrated. Purification on silica gel eluting with hexane/EtOAc 4:1 afforded viscous yellow oil (14.6 g, 66 %): ¹H NMR (300 MHz, CDCl₃) δ 5.66 (d, *J* = 13.7 Hz, 6H), 1.24 (s, 27H) ppm; ³¹P NMR (120 MHz, CDCl₃) δ -4.74 (s) ppm; HRMS (M+H⁺) calculated for C₁₈H₃₄O₁₀P 441.1890, found 441.1901.

Preparation of Bis(POM) hydrogen phosphate



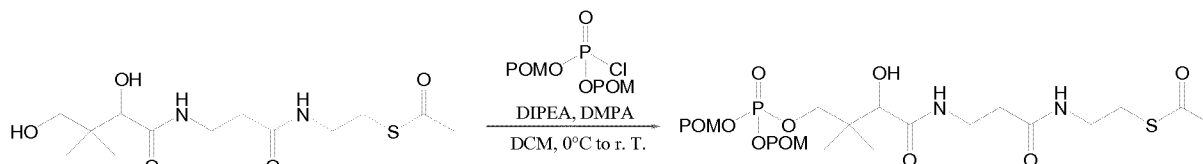
Tris(POM) phosphate (1 g, 2.3 mmol) was dissolved in piperidine (7 mL) and stirred at room temperature for 12 h. The solution was concentrated and further evaporated in vacuo until constant weight. (935 mg, 99.0% yield). The crude oil (935 mg, 2.28 mmol) was dissolved in water (20 ml) and treated with Dowex W50X2 H⁺ form resin (19.2 g, 11.4 mmol, 0.6 mmol/g). The suspension was stirred at ambient temperature for 1 hour. The resin was filtered and washed with water. The filtrate was concentrated and dried in vacuo affording a white solid (613 mg, 82% yield): ¹H NMR (300 MHz, CDCl₃) δ 8.45 (bs, 1H), 5.62 (d, *J* = 13.2 Hz, 4H), 1.23 (s, 18H) ppm; ³¹P NMR (120 MHz, CDCl₃) δ -3.17 (s) ppm.

10 Preparation of Bis(POM) chloro phosphate



A solution of bis(POM) hydrogen phosphate (613 mg, 1.88 mmol) and DMF (7.3 μL, 0.094 mmol) in DCM (7.5 mL) was added dropwise to a stirred solution of oxalyl chloride (889 μL, 9.38 mmol) in DCM (7.5 mL) under argon at ambient temperature. Reaction mixture was stirred for 2 hours. The solvent was evaporated under argon to provide a crude yellow oil (671 mg, 1.86 mmol) which was directly used in the next step.

Preparation of S-acetyl phosphopantetheine bis[(pivaloyloxy)methyl] ester

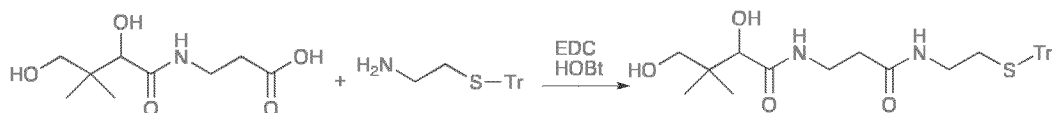


S-acetyl-pantetheine was prepared as described in [E. Walton et al., J. Am. Chem. Soc. 1954, 76, 1146]. To a stirred solution of S-acetyl-pantetheine (463 mg, 1.45 mmol), *N,N*-isopropylethylamine (308 μL, 1.77 mmol) and 4-Dimethylaminopyridine (10.9 mg, 0.09 mmol) in 10 ml of DCM at 0 °C, was added dropwise under argon a solution of bis(POM) chloro phosphate (590 mg, 1.88 mmol) in 10 ml of DCM. Reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The reaction was quenched with water (10 ml) and extracted with DCM (2 x 20 ml). Organic phase was washed with saturated solution of NH₄Cl, dried over Na₂SO₄ and concentrated under reduced pressure. Purification on silica gel eluting with DCM/MeOH, 92:8 afforded the product as a yellow oil (401 mg, 44% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.25 (app t, *J* = 6.2 Hz, 1H), 6.39 (app t, *J* = 5.3 Hz, 1H), 5.61-5.71 (m, 4H), 4.13 (dd, *J* = 10.0, 6.9 Hz, 1H), 4.08 (d, *J* = 6.3 Hz, 1H), 3.97 (d, *J* = 5.8 Hz, 1H), 3.75 (dd, *J* = 10.0, 7.2 Hz, 1H), 3.51-3.63 (m, 2H), 3.34-3.50 (m, 2H), 2.95-3.09 (m, 2H), 2.39-2.47 (m, 2H), 2.35 (s, 3H), 1.242 (s, 9H), 1.240 (s, 9H), 1.12 (s, 3H), 0.88 (s, 3H) ppm; ³¹P NMR (120 MHz, CDCl₃) δ -2.64 (s) ppm.

Example 9: Alternative method for the synthesis of 4'-phosphopantetheine

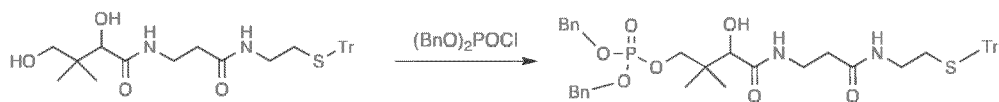
D-Pantothenic acid was prepared from its hemicalcium salt (Aldrich, $\geq 99.0\%$) reacting with oxalic acid. S-Tritylcysteamine was synthesized from cysteamine hydrochloride and trityl chloride as reported by Mandel et al. [A. L. Mandel, et al., *Org. Lett.* 2004, 6, 26, 4801-4803]. Dibenzylchlorophosphate was prepared by reacting dibenzylphosphite with N-chlorosuccinimide as described by Itoh et al. [K. Itoh et al., *Org. Lett.* 2007, 9, 5, 879-882] in toluene as a solvent. All other chemicals were obtained from commercial sources and used without further purification; cysteamine hydrochloride (Aldrich, $\geq 98.0\%$), trityl chloride (Aldrich, 97.0 %), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (Aldrich, $\geq 97.0\%$), 1-hydroxybenzotriazole hydrate (Aldrich, $\geq 97.0\%$), dibenzylphosphite (Aldrich, technical grade), N-chlorosuccinimide (Aldrich, 98 %). Column chromatography was carried out using Silica gel 60 Å, 60-100 mesh (Aldrich). Cation exchange chromatography was performed on DOWEX 50WX2, hydrogen form, 100-200 mesh (Aldrich). ^1H and ^{13}C NMR were recorded at 25 °C with Varian Unity Inova 300 MHz spectrometer (300 MHz/75 MHz). The chemical shifts (δ) are reported in ppm units relative to TMS as an internal standard where spectra recorded in CDCl_3 or relative to residual solvent signal when D_2O was used. High-resolution mass spectra were obtained on AutospecQ mass spectrometer with negative electrospray ionization.

a) Coupling reaction – synthesis of S-tritylpantetheine



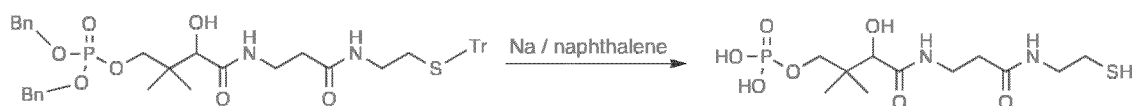
In dried acetonitrile (100 mL) were prepared separately: (A) D-pantothenic acid (2.19 g, 10.0 mmol), (B) S-tritylcysteamine (3.19 g, 10.0 mmol) and (C) N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (1.55 g, 10.0 mmol) together with 1-hydroxybenzotriazole hydrate (1.35 g, 10.0 mmol). When mixed together (A), (B) and (C), triethylamine (10.4 mL, 75 mmol) was added. The mixture was stirred at room temperature for 24 h and quenched with addition of water. The product was extracted with diethyl ether. The combined organic phases were washed with 1 M hydrochloric acid, saturated aqueous solution of NaHCO_3 and brine. Organic layer was dried over sodium sulfate and concentrated in vacuum to give S-tritylpantetheine (3.53 g, 68 %) as pale-yellow crystals. ^1H NMR (300 MHz, CDCl_3) δ 0.85 (s, 3H), 0.92 (s, 3H), 2.29 (t, $J = 6.2$ Hz, 2H), 2.38 (t, $J = 6.4$ Hz, 2H), 3.03 (dd, $J = 6.0, 5.2$ Hz, 2H), 3.45 (m, 4H), 3.92 (s, 1H), 6.20 (t, $J = 5.7$ Hz, 1H, NH), 7.21 (m, 3H), 7.27 (m, 6H), 7.39 (m, 6H).

b) Phosphorylation – synthesis of S-trityl-4'-dibenzylphosphopantetheine



Dibenzylchlorophosphate was freshly prepared by reaction of dibenzylphosphite (2.16 g, 8.24 mmol) with N-chlorosuccinimide (1.21 g, 9.06 mmol) in toluene (40 mL) at room temperature for 2 h. The mixture was filtered and the filtrate was evaporated under vacuum and added to a solution of S-tritylpantetheine (2.86 g, 5.49 mmol), diisopropylethylamine (3.06 mL), 4-dimethylaminopyridine (0.067 g, 0.55 mmol) in dry acetonitrile. The mixture was stirred for 2 h at room temperature. Products were extracted into organic phase in dichloromethane – aqueous NaHCO₃ system. The organic extracts were washed with water and brine, and dried over Na₂SO₄. Evaporation of solvent gave a crude S-trityl-4'-dibenzylphosphopantetheine as a dark brown oil (4.69 g), which was further purified by flash chromatography to give a semicrystalline pale yellow product (0.640 g, 0.82 mmol). The yield of the synthesis and purification of S-trityl-4'-dibenzylphosphopantetheine is 15 %. ¹H NMR (300 MHz, CDCl₃) δ 0.75 (s, 3H), 1.03 (s, 3H), 2.32 (t, J = 6.1 Hz, 2H), 2.4 (t, J = 6.5 Hz, 2H), 3.06 (dd, J = 6.5, 6.2 Hz, 2H), 3.47 (dd, J = 6.1, 6.0 Hz, 2H), 3.60 (dd, J = 9.9, 7.3 Hz, 1H), 3.85 (s, 1H), 4.00 (dd, J = 9.9, 7.0 Hz, 1H), 5.04 (m, 4H), 5.80 (t, J = 5.5 Hz, 1H, NH), 7.18-7.42 (m, 25H).

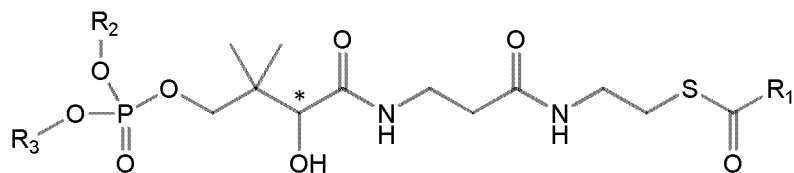
c) Deprotection – synthesis of 4'-phosphopanetheine



Naphthalene (12.9 g, 100.6 mmol) dissolved in tetrahydrofuran (70 mL) was added to sodium metal (2.21 g, 96.1 mmol) in tetrahydrofuran (50 mL). After 2 h the solution was cooled to $-(35 \pm 5)$ °C and S-trityl-4'-dibenzylphosphopantetheine (1.85 g, 2.37 mmol) dissolved in tetrahydrofuran (70 mL) was slowly added. The mixture was stirred for a 2 h while maintaining the temperature below -30 °C. The reaction was quenched by addition of water and then dichloromethane was added. Aqueous phase was washed with dichloromethane and diethylether, concentrated under vacuum and passed through cation exchange column (DOWEX 50WX2). Fractions were analyzed by LCMS and those containing the product were pooled and concentrated under vacuum. 4'-phosphopanetheine was precipitated with addition of Ca(OH)₂ as a calcium salt (332 mg, 0.838 mmol, 35 %). The structure of the product was confirmed by comparison of NMR data with the literature [Lee, C-H. et al., J. Am. Chem. Soc. 1975, 1225-1236] and by HRMS. ¹H NMR (300 MHz, D₂O) δ 0.86 (s, 3H), 1.08 (s, 3H), 2.54 (t, J = 6.3 Hz, 2H), 2.87 (t, J = 6.3 Hz, 2H), 3.43 (dd, J = 10.3, 5.0 Hz, 1H), 3.54 (m, 4H), 3.76 (dd, J = 10.3, 6.5 Hz, 1H), 4.14 (s, 1H). The HRMS mass for C₁₁H₂₂N₂O₇SP [M-H]⁻ was found to be 357.0880, which corresponds to the expected mass of 357.0885.

Claims

1. A compound having the structural formula:



(Structure I),

5 wherein:

R₁ is -H, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₁₁, -C(O)OR₁₁, -C(O)NR₁₁R₁₂, -C=NR₁₁, -CN, -OR₁₁, -OC(O)R₁₁, -NR₁₁R₁₂, -NR₁₁C(O)R₁₂, -NO₂, -N=CR₁₁R₁₂ or -halogen; preferably C₁-C₁₀ alkyl, more preferably -methyl, -ethyl, -propyl or -butyl, such as *t*-butyl, most preferred -methyl;

R₂ and **R₃** are independently selected from the group consisting of: -methyl, -ethyl,

-phenyl, acetoxymethyl (AM), pivaloyloxymethyl (POM), ,

15 , , , , ; or

R₂ and **R₃** jointly form a structure selected from the group consisting of:

and ; wherein

R₄ is -H or -alkyl, preferably -methyl;

20 **R₅** is -H or -alkyl, preferably -methyl or *t*-butyl;

R₆ is -H, -alkyl, or -CH₂(CO)OCH₃;

R₇ is -H, -alkyl or -halogen;

R₈ is -H, -alkyl, preferably *t*-butyl;

R₉ is -H, -alkyl, preferably -methyl or *t*-butyl;

R₁₀ is -H, -alkyl, preferably -methyl or *t*-butyl;

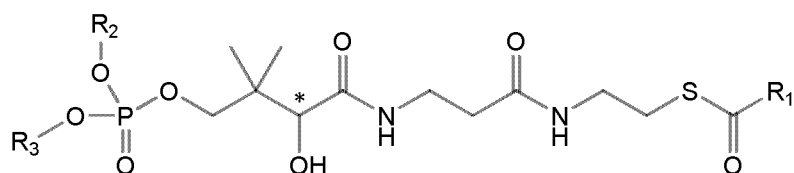
R₁₁ and **R₁₂** are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, or halogen;

with the proviso that the compound is not (S)-acetyl-4'-phosphopantetheine or (S)-benzoyl-4'-phosphopantetheine;

or a pharmaceutically acceptable salt or solvate thereof.

2. The compound of claim 1, wherein **R₂** and **R₃** are identical residues.

3. A compound having the structural formula:



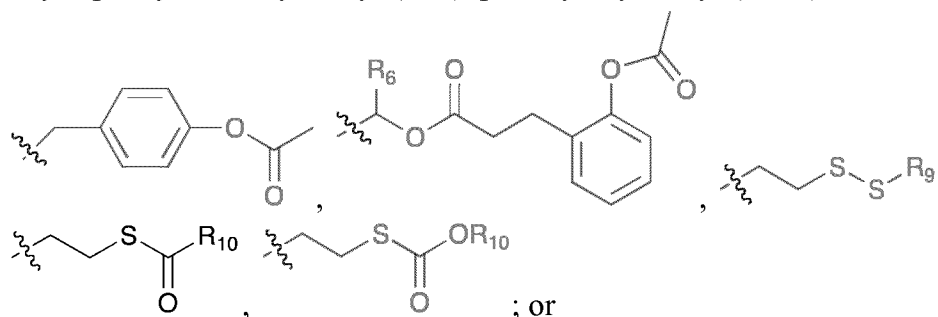
(Structure I),

wherein:

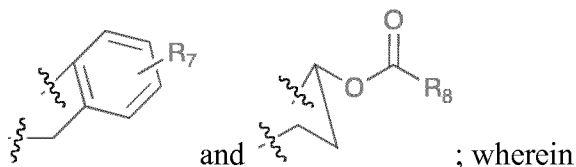
R₁ is -H, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted aromatic heterocyclyl, substituted or unsubstituted heterocyclylalkyl, -COR₁₁, -C(O)OR₁₁, -C(O)NR₁₁R₁₂, -C=NR₁₁, -CN, -OR₁₁, -OC(O)R₁₁, -NR₁₁R₁₂, -NR₁₁C(O)R₁₂, -NO₂, -N=CR₁₁R₁₂ or -halogen; preferably C₁-C₁₀ alkyl, more preferably -methyl, -ethyl, -propyl or -butyl, for example *t*-butyl, most preferred -methyl;

R₂ and **R₃** are independently selected from the group consisting of: -H, -methyl, -

ethyl, -phenyl, acetoxymethyl (AM), pivaloyloxymethyl (POM),



R₂ and **R₃** jointly form a structure selected from the group consisting of:



R₄ is -H or -alkyl, preferably -methyl or *t*-butyl;

R₅ is -H or -alkyl, preferably C₁-C₄ alkyl, most preferably -methyl, or *t*-butyl;

5 **R₆** is -H, -alkyl or -CH₂(CO)OCH₃;

R₇ is -H or -alkyl or -halogen;

R₈ is -H or -alkyl, preferably *t*-butyl;

R₉ is -H, -alkyl, preferably C₁-C₄ alkyl;

R₁₀ is -H, -alkyl, preferably C₁-C₄ alkyl;

10 **R₁₁** and **R₁₂** are each independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy or halogen;

or a pharmaceutically acceptable salt or solvate thereof;

15 for use as a medicament.

4. The compound for use as a medicament of claim 3, wherein said medicament is useful in the treatment of a neurodegenerative disease, epilepsy or cancer.

5. The compound for use as a medicament of claim 4, wherein said neurodegenerative disease is pantothenate kinase-associated neurodegeneration (PKAN).

20 6. Method of producing the compound of claims 1 or 3, said method comprising the step of reacting 4'-phosphopantothenate with an (S)-substituted mercaptoethylamine to yield (S)-substituted-4'-phosphopantetheine.

7. Method of claim 6 wherein said (S)-substituted mercaptoethylamine is (S)-trityl mercaptoethylamine or (S)-benzyl mercaptoethylamine; and said (S)-substituted-4'-phosphopantetheine is (S)-trityl-4'-phosphopantetheine or (S)-benzyl-4'-phosphopantetheine.

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8. Method of claim 6 or 7 comprising enzymatic conversion of pantothenate to 4'-phosphopantothenate prior to the step of reacting 4'-phosphopantothenate with an (S)-substituted mercaptoethylamine to yield (S)-substituted-4'-phosphopantetheine.

30 9. Method of claim 8 further comprising converting said (S)-substituted-4'-phosphopantetheine to 4'-phosphopantetheine.

10. Method of claim 9 further comprising converting said 4'-phosphopantetheine by thioesterification to (S)-acyl-4'-phosphopantetheine.

11. Method of claim 10, further comprising formation of a phosphate ester of said (S)-acyl-4'-phosphopantetheine with a halomethyl ester of a carboxylic acid.

5 12. Method of producing the compound of claims 1 or 3, said method comprising the steps of a) reacting pantothenate with an (S)-substituted mercaptoethylamine to yield (S)-substituted pantetheine, b) reacting the S-substituted pantetheine with a phosphorylating agent to obtain a phosphate ester of S-substituted 4'-phosphopantetheine and c) converting said phosphate ester of (S)-substituted-4'-
10 phosphopantetheine to 4'-phosphopantetheine.

13. Method of claim 12 wherein said (S)-substituted mercaptoethylamine is (S)-trityl mercaptoethylamine or (S)-benzyl mercaptoethylamine; and said phosphate ester of (S)-substituted-4'-phosphopantetheine is (S)-trityl-4'-dibenzylphosphopantetheine or (S)-benzyl-4'-dibenzylphosphopantetheine.

15 14. Method of claim 13 further comprising converting said (S)-substituted-4'-phosphopantetheine to 4'-phosphopantetheine and further comprising converting said 4'-phosphopantetheine by thioesterification to (S)-acyl-4'-phosphopantetheine.

15. Method of claim 14, further comprising formation of a phosphate ester of said (S)-acyl-4'-phosphopantetheine with a halomethyl ester of a carboxylic acid.

20 16. Method of producing the compound of claims 1 or 3, said method comprising the step of reacting the (S)-substituted pantetheine with a phosphorylating agent to obtain a phosphate ester of S-substituted 4'-phosphopantetheine

25 17. Method of claim 16 wherein said (S)-substituted pantetheine is (S)-acylpantetheine; and said phosphate ester of (S)-substituted-4'-phosphopantetheine is bis(pivaloyloxymethyl) ester of (S)-acyl-4'-phosphopantetheine

* * * * *

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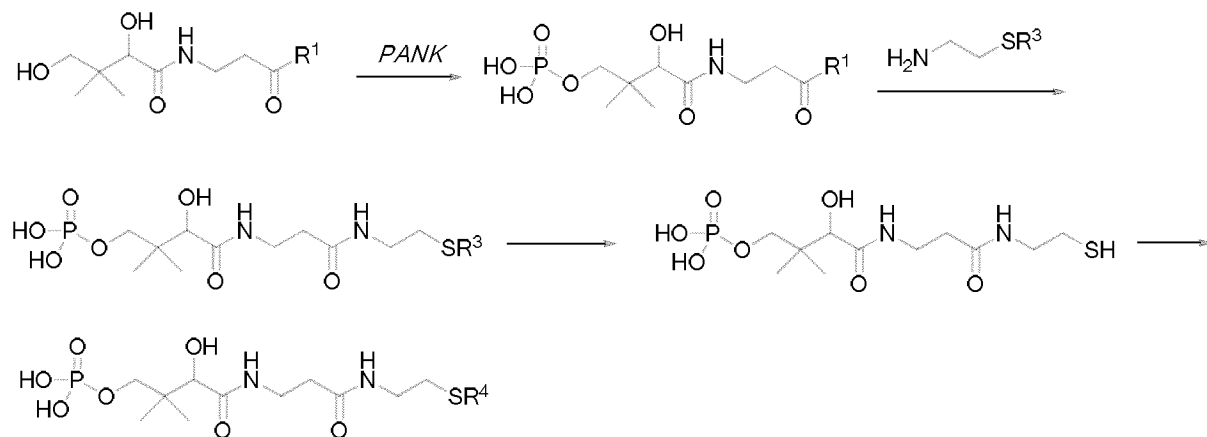


FIG. 1

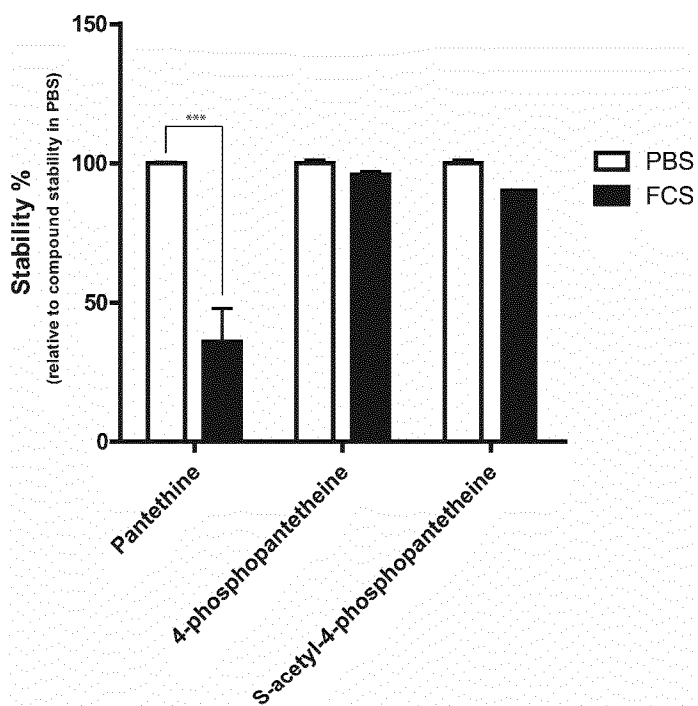


FIG. 2

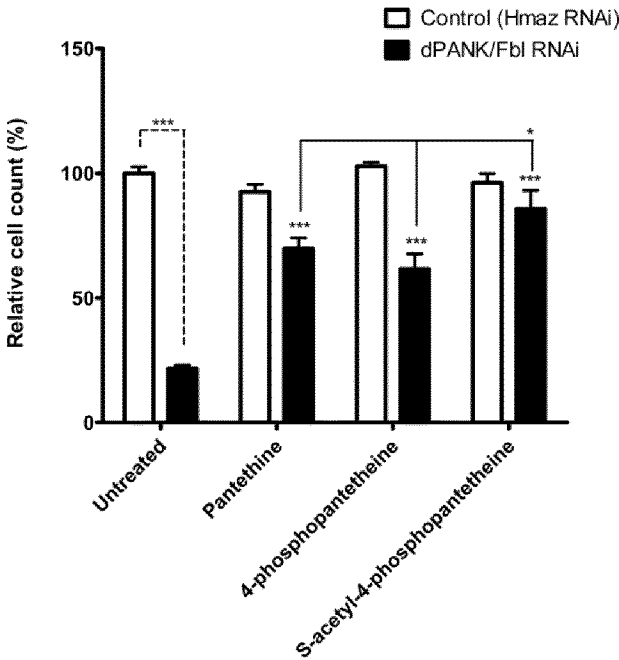


FIG. 3

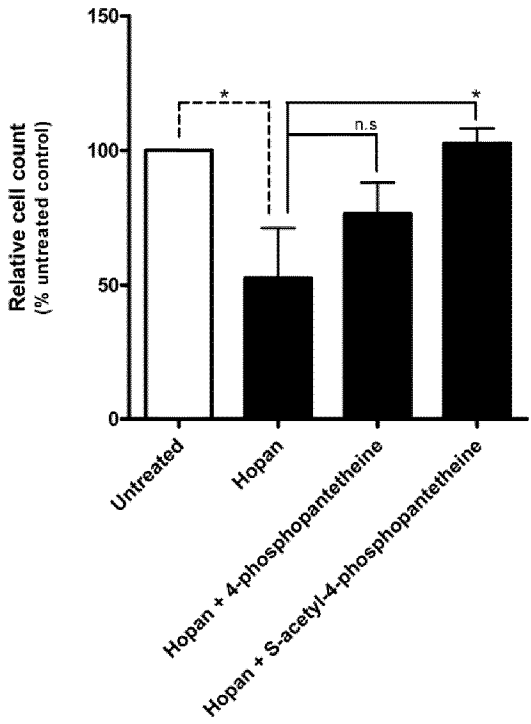


FIG. 4

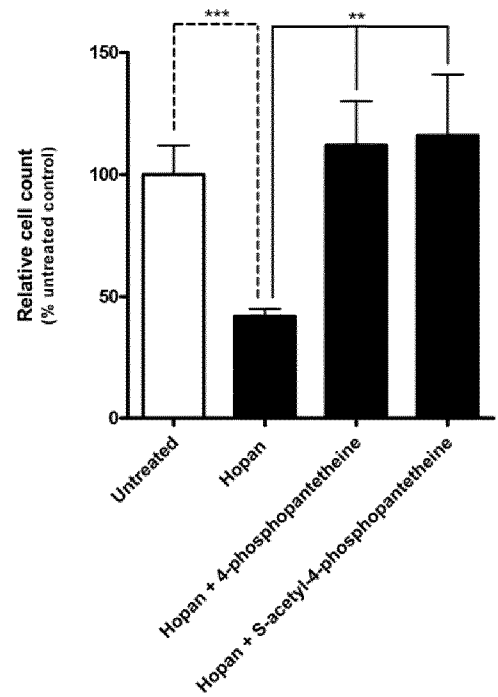


FIG. 5

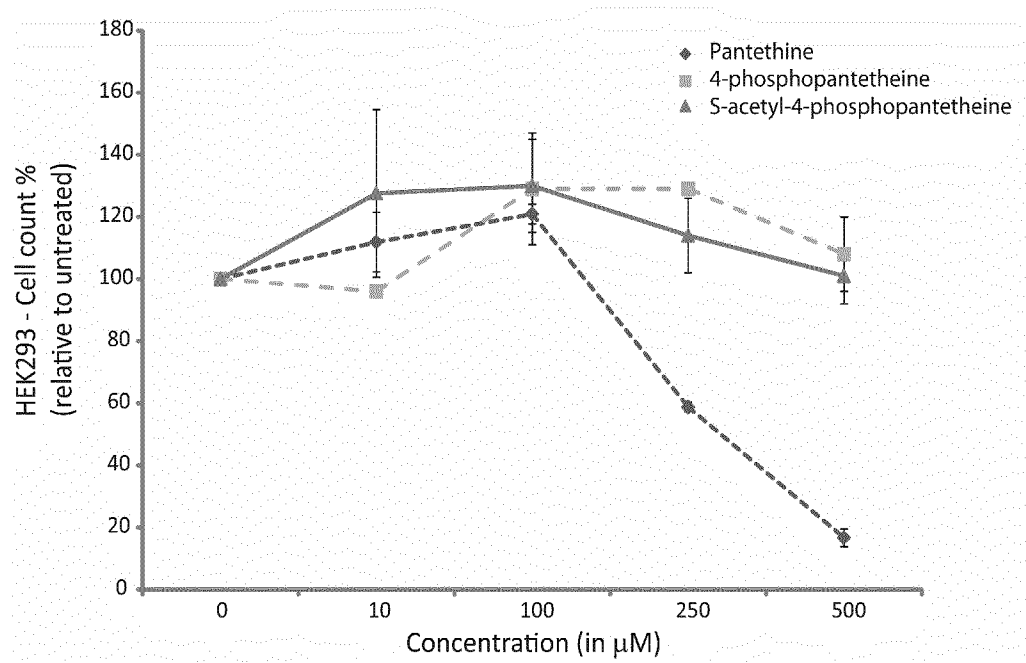


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/073258

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07F9/09 A61K31/661 A61P25/28
ADD.

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 A61K A61P

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)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ZHHAO ZHUANG ET AL: "Divergence of Function in the Hot Dog Fold Enzyme Superfamily: The Bacterial Thioesterase YciA +", BIOCHEMISTRY, vol. 47, no. 9, 1 March 2008 (2008-03-01), pages 2789-2796, XP055101787, ISSN: 0006-2960, DOI: 10.1021/bi702334h n-butyryl-pantetheinephosphate; page 2793; tables 1,2</p> <p>-----</p> <p>-/--</p>	1-5



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 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

1 December 2014

Date of mailing of the international search report

23/12/2014

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Fax: (+31-70) 340-3016

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Duval, Eric

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/073258

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>NIKAWA J I ET AL: "Inhibitory effects of long-chain acyl coenzyme a analogues on rat liver acetyl coenzyme a carboxylase", FEBS LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 102, no. 2, 15 June 1979 (1979-06-15), pages 223-226, XP025593681, ISSN: 0014-5793, DOI: 10.1016/0014-5793(79)80005-8 [retrieved on 1979-06-15] palmitoyl-4'-phosphopantetheine; page 224; table 1</p> <p>-----</p>	1-5
A	<p>JANINE G. BORGARO ET AL: "Substrate Recognition by [beta]-Ketoacyl-ACP Synthases", BIOCHEMISTRY, vol. 50, no. 49, 13 December 2011 (2011-12-13), pages 10678-10686, XP055101944, ISSN: 0006-2960, DOI: 10.1021/bi201199x page 10681; compound 4</p> <p>-----</p>	1-5
A	<p>CRAIG M. BARTLING ET AL: "Steady-State Kinetics and Mechanism of LpxD, the N-Acyltransferase of Lipid A Biosynthesis +", BIOCHEMISTRY, vol. 47, no. 19, 1 May 2008 (2008-05-01), pages 5290-5302, XP055101959, ISSN: 0006-2960, DOI: 10.1021/bi800240r (R)-3-Hydroxy-lauroyl-methylphosphopantetheine; page 5295</p> <p>-----</p>	1-5
A	<p>LUSONG LUO ET AL: "Role of Active Site Binding Interactions in 4-Chlorobenzoyl-Coenzyme A Dehalogenase Catalysis +", BIOCHEMISTRY, vol. 40, no. 51, 1 December 2001 (2001-12-01), pages 15684-15692, XP055101963, ISSN: 0006-2960, DOI: 10.1021/bi011536f 4-CBA-pantethiene phosphate; page 15688</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-5

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/073258

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>L. HOFFMANN: "Identification of the Enzymatic Active Site of Tobacco Caffeoyl-coenzyme A O-Methyltransferase by Site-directed Mutagenesis", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 276, no. 39, 17 July 2001 (2001-07-17), pages 36831-36838, XP055102076, ISSN: 0021-9258, DOI: 10.1074/jbc.M104977200 caffeoylphosphopantetheine; page 36835; figure 3</p> <p>-----</p>	1-5
A	<p>GERNGROSS T U ET AL: "ENZYME-CATALYZED SYNTHESIS OF POLY[(R)-(-)-3-HYDROXYBUTYRATE]: FORMATION OF MACROSCOPIC GRANULES IN VITRO", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 92, no. 14, 3 July 1995 (1995-07-03), pages 6279-6283, XP000674211, ISSN: 0027-8424, DOI: 10.1073/PNAS.92.14.6279 page 6280; compounds 9, 5</p> <p>-----</p>	1-5
A	<p>D. K. SRIVASTAVA ET AL: "'Dehydrogenase" and "Oxidase" Reactions of Medium-Chain Fatty Acyl-CoA Dehydrogenase Utilizing Chromogenic Substrates: Role of the 3',5'-Adenosine Diphosphate Moiety of the Coenzyme A Thioester in Catalysis", BIOCHEMISTRY, vol. 34, no. 14, 1 April 1995 (1995-04-01), pages 4625-4632, XP055102083, ISSN: 0006-2960, DOI: 10.1021/bi00014a016 Indolepropionyl / Indoleacryloyl Pantetheine Phosphate; page 4627</p> <p>-----</p>	1-5
A	<p>NEGREL J ET AL: "The biosynthesis of feruloyltyramine in Nicotiana tabacum", PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 23, no. 12, 1 January 1984 (1984-01-01), pages 2797-2801, XP026609325, ISSN: 0031-9422, DOI: 10.1016/0031-9422(84)83018-6 [retrieved on 1984-01-01] feruloyl-4'-phosphopantetheine; page 2799</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-5

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/073258

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JONATHAN NEGREL ET AL: "The phosphohydrolysis of hydroxycinnamoyl-coenzyme a thioesters in plant extracts", PHYTOCHEMISTRY, vol. 23, no. 1, 1 January 1984 (1984-01-01), pages 31-34, XP055102088, ISSN: 0031-9422, DOI: 10.1016/0031-9422(84)83072-1 p-Coumaroyl-4'-phosphopantetheine; page 32; table 1 -----	1-5
A	WO 2012/017400 A1 (UNIV NORTHWEST [ZA]; VAN DIJK ALBERDINA AIKE [ZA]; BADENHORST CHRISTOF) 9 February 2012 (2012-02-09) cited in the application S-benzoyl-4'-phosphopantetheine; page 25 claim 5 -----	1-5
A	ANNICK MÉJEAN ET AL: "-Proline to Acyl Carrier Protein Bound Dehydroproline", BIOCHEMISTRY, vol. 49, no. 1, 12 January 2010 (2010-01-12), pages 103-113, XP055102139, ISSN: 0006-2960, DOI: 10.1021/bi9018785 page 110; compounds F4, F8 -----	1-5
A	WO 03/008626 A2 (UNIV OREGON HEALTH & SCIENCE [US]; UNIV CALIFORNIA [US]; HAYFLICK SUSA) 30 January 2003 (2003-01-30) cited in the application page 35 -----	3-5
A	WO 2013/163576 A1 (RETROPHIN INC [US]; VAINO ANDREW [US]; BIESTEK MAREK [US]; SHKRELI MAR) 31 October 2013 (2013-10-31) claims 1, 8 -----	3-5
A	GB 749 715 A (ROCHE PRODUCTS LTD) 30 May 1956 (1956-05-30) example 8 ----- -/--	6-17

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2014/073258

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ALEXANDER L. MANDEL ET AL: "Modular Synthesis of Pantetheine and Phosphopantetheine", ORGANIC LETTERS, vol. 6, no. 26, 1 December 2004 (2004-12-01), pages 4801-4803, XP055102188, ISSN: 1523-7060, DOI: 10.1021/ol048853+ figure 1 scheme 2	6-11
A	KATARZYNA SIUDEJA ET AL: "Impaired Coenzyme A metabolism affects histone and tubulin acetylation in Drosophila and human cell models of pantothenate kinase associated neurodegeneration", EMBO MOLECULAR MEDICINE, vol. 3, no. 12, 14 October 2011 (2011-10-14), pages 755-766, XP055101756, ISSN: 1757-4676, DOI: 10.1002/emmm.201100180 the whole document	1-11
A	AARON G. RABINKOV ET AL: "Interaction of acetyl-CoA fragments with rat liver acetyl-CoA carboxylase", EUROPEAN JOURNAL OF BIOCHEMISTRY, vol. 193, no. 2, 1 October 1990 (1990-10-01), pages 351-353, XP055101772, ISSN: 0014-2956, DOI: 10.1111/j.1432-1033.1990.tb19345.x the whole document	1
A	SCOTT J HECKER AND MARK D ERION: "Prodrugs of Phosphates and Phosphonates", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 51, no. 8, 24 April 2008 (2008-04-24), pages 2328-2345, XP008148502, ISSN: 0022-2623, DOI: 10.1021/JM701260B [retrieved on 2008-02-01] the whole document	1-11
A	HWANG ET AL: "Enzymatic and cellular study of a serotonin N-acetyltransferase phosphopantetheine-based prodrug", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 15, no. 5, 31 January 2007 (2007-01-31), pages 2147-2155, XP005867179, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2006.12.016 page 2149; compounds 2,3	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/073258

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.:
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:

see additional sheet

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 an 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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-17

compounds of formula (1) per se as well as for therapeutic use, and method for their preparation

1.1. claims: 1-5

compounds of formula (1) per se and for therapeutic use

1.2. claims: 6-15

process for the preparation of compounds of formula (I) involving (S)-substituted mercaptoethylamine

1.3. claims: 16, 17

process for the preparation of the compounds of formula (I) comprising the phosphorylation of S-substituted pantetheine into a phosphate ester of S-substituted 4'-phosphopantetheine

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/073258

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012017400	A1	09-02-2012	NONE
WO 03008626	A2	30-01-2003	AU 2002326412 A1 03-03-2003 WO 03008626 A2 30-01-2003
WO 2013163576	A1	31-10-2013	AU 2013251345 A1 27-11-2014 US 2013289001 A1 31-10-2013 US 2014135294 A1 15-05-2014 WO 2013163576 A1 31-10-2013
GB 749715	A	30-05-1956	BE 532299 A 01-12-2014 CH 329575 A 30-04-1958 DE 961171 C 04-04-1957 FR 1110939 A 20-02-1956 GB 749715 A 30-05-1956