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(54) Title: NEURODEGENERATIVE PEPTIDE DEPOSIT DISSOLUTION

(57) Abstract: The invention pertains to a prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer, for use in a method of treating a medical condition characterized by the presence of deposits of neuropath ological peptides. The prodrug is selected from an ester of a bisphosphonate or an ester of a calcium chelating compound, and the medical condition characterized by the presence of deposits of neuropath ological peptides can be Alzheimer's disease, Parkinson's disease or Huntington's disease.

Title: Neurodegenerative peptide deposit dissolution

Field of invention

The present disclosure relates generally to an ester prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound, for use in the treatment of conditions characterized by the presence of deposits of neuropathological peptides, in particular to prevent, reverse and cure the development neurodegenerative diseases such as Alzheimer's, Parkinson and Huntington.

Background of the invention

Neurodegenerative conditions are characterized by the development of pathological processes years before clinical symptoms become prevalent. These pathological processes eventually lead to a cascade of neurotoxic processes which slowly damage the functioning of the brain. Eventually, this reaches the point where brain functioning is hampered to that extent that the patient will experience clinical symptoms.

Neurodegenerative diseases have a common trait in the sense that they are all linked to elevated production of certain neurodegenerative proteins. For reasons yet unknown, these proteins aggregate in brain, leading to deposits that are neurotoxic.

The pathological processes of neurodegenerative conditions are still largely unknown but in the last decades it has been discovered that a plethora of proteins might be of high relevance to the development of these diseases.

Alzheimer's disease is a neurodegenerative condition characterized by the abundance of amyloid beta (Abeta). Abeta is a neurotoxin and the

accumulation of Abeta induces toxic oligomers and fibrils which causes impairment of synapses and neurons. Several drugs have been developed to prevent the generation of Abeta, its aggregation or promote its clearance. Beta and Gamma secretase inhibitors and modulators decrease formation of abeta out of amyloid precursor protein (APP) and are in development as anti alzheimer's drugs.

Another approach to decrease Abeta aggregations are drugs that would prevent aggregation. These strategies act by either binding to abeta monomers to prevent oligomerization, or by reaction with abeta oligomers thereby elevating their toxicity and hence promoting their clearance.

Tau is another protein that is thought to be of high relevance in the development of Alzheimer's disease. Tau is highly abundant in the brain and neurons, and plays a crucial role in the formation and stabilization of microtubules.

Parkinson's disease (PD) is a neurodegenerative condition characterized by a gradual loss of dopaminergic neuron of the nigrostriatal pathway. Over the last two decades, alpha synuclein (asyn) has been found to be a relevant protein in the pathology of PD. Although the physiological function of asyn is not completely elucidated, it is thought to be implicated in modulating synaptic activity through regulation of synaptic-vesicle release. Asyn is a 14 kDa protein and it exists in various conformational shapes and oligomeric states. The fibrillation is under constant influence of factors that accelerate or inhibit formation. In PD the presence of intraneuronal proteinaceous cytoplasmatic inclusions called Lewis bodies (LB) and dystrophy Lewy neurites (LN) are present, which contain asyn deposits. The mechanism that leads to the formation of these inclusions is still unknown.

Two approaches are pursued to decrease asyn. The first approach is to decrease synthesis by silencing of expression with for instance RNAi. A second approach is to increase the clearance of asyn. Increasing proteasomal or lysosomal activity appears a viable possibility. Alternatively increasing autophagy by small molecules is another approach to increase clearance.

Huntington's disease is neurodegenerative condition that is caused by an elongated polyglutamine tract. It is characterized by neuronal dysfunction followed by loss of medium spiny neurons in striatum.

Multiple other neurodegenerative diseases exist, which all are characterized by formation of protein deposits, that leads to neurotoxic aggregates. The cause of formation of such deposits is as yet unknown.

Summary of the invention

The inventors have found that it is possible to treat neurodegenerative diseases characterized by the presence of deposits of neuropathological peptides by administration of a prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound. The inventors found that calcium ion or magnesium ion binds to phosphorylation sites of protein, which reduces the solubility of the protein and leads to formation of a protein deposit. The protein deposit in turn leads to the characteristic symptoms of the disease. The inventors have found that by administration of a calcium ion or magnesium ion solubilizer, calcium ion is at least partially removed from the protein deposit, which leads to increased solubility of the protein in the protein deposit, and results in increased clearance of the deposit, resulting in a treatment of the neurodegenerative disease.

By administration of a prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound, the calcium ion or magnesium ion solubilizer can pass the blood brain barrier, whereupon the calcium ion or magnesium ion solubilizer is liberated by endogenous enzymes, thereby increasing the clearance of peptide deposits in the brain.

Detailed description of the invention

The invention pertains to a prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound, for use in a method of treating a medical condition characterized by the presence of deposits of neuropathological peptides.

The medical condition characterized by the presence of deposits of neuropathological peptides is a condition, in which the symptoms or effects of the condition are caused directly or indirectly by formation of insoluble protein deposits in neurological pathways, preferably in the brain and behind the blood brain barrier. A variety of such conditions are known. Important examples of conditions to be treated according to the invention include Alzheimer's disease, Parkinson's disease or Huntington's disease.

Alzheimer's disease is characterized by the presence of deposits of amyloid beta (abeta) and/or TAU protein. Parkinson's disease is a condition characterized by the presence of deposits of alpha synuclein peptide ("asyn deposits").

The inventors have found that the insoluble peptide deposits are formed with peptides that have at least a certain degree of phosphorylation. In much preferred embodiments, the condition characterized by the presence of

deposits of neuropathological peptides is a condition in which the protein deposits comprise phosphorylated protein.

Protein phosphorylation, principally on serine, threonine or tyrosine residues, is one of the most important post-translational modifications. Phosphorylation plays critical roles in the regulation of many cellular processes including cell cycle, growth, apoptosis and signal transduction pathways. For a large subset of proteins, phosphorylation is tightly associated with protein activity and is a key point of protein function regulation. Phosphorylation regulates protein function and cell signaling by causing conformational changes in the phosphorylated protein.

Without wishing to be bound by theory, the inventors currently believe that protein deposits formed from phosphorylated proteins are rendered insoluble by the action of calcium ion or magnesium ion. It has been found that conditions characterized by the presence of deposits of neuropathological peptides can be treated by administration of an ester prodrug for a calcium ion or magnesium ion solubilizer as defined below. Preferably, treatment is achieved by a calcium ion solubilizer.

The calcium ion or magnesium ion solubilizer is a molecule that has significant affinity for calcium ions and thereby effectively competes for binding of calcium with other calcium binding molecules. Thus, a calcium ion or magnesium ion solubilizer in accordance with the present invention is a compound which binds calcium under physiological conditions.

Calcium ion is defined herein as Ca^{2+}. Calcium ion is abundantly present in the body. Typical calcium extracellular concentrations are 1-5 mM. Intracellular calcium concentrations are much lower at generally 100 nM, but may reach levels up to 10000 nM depending on cell function and status.

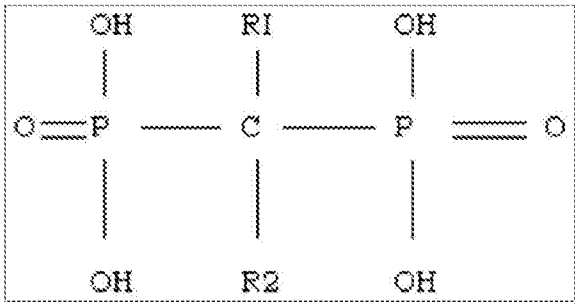
Presence of a calcium ion or magnesium ion solubilizer at an insoluble peptide deposit has the effect of dissolving calcium ion from the insoluble peptide deposit, thereby liberating peptides from the deposit and enhancing dissolution of the peptide, which results in clearance of the deposit. Thus, diseases characterized by the presence of deposits of neuropathological peptides can be treated with a compound which is a calcium ion or magnesium ion solubilizer. In order to obtain increased presence of the calcium ion or magnesium ion solubilizer at the peptide deposit, it is presently disclosed that an ester prodrug for a calcium ion or magnesium ion solubilizer allows for increased local concentration of the calcium ion or magnesium ion solubilizer at the peptide deposit, due to enhanced efficiency in passing the blood brain barrier.

The calcium ion or magnesium ion solubilizer is physiologically acceptable. This means that the calcium ion or magnesium ion solubilizer can be administered to living organisms. The calcium ion or magnesium ion solubilizer should be able to be dosed in humans and animals at concentrations that do not exert side effects that exceed the clinical benefit of the compound.

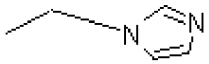
The calcium ion or magnesium ion solubilizer can be any known calcium ion or magnesium ion solubilizer. A calcium ion solubilizer is preferred. Preferably, the calcium ion or magnesium ion solubilizer is selected from the group consisting of a bisphosphonate and a calcium chelating compound.

Bisphosphonates are typically used for the treatment of osteoporosis, osteitis deformans (Paget's disease of the bone), bone metastasis (with or without hypercalcaemia), multiple myeloma, and other conditions involving fragile, breakable bone osteoporosis and related diseases.

A bisphosphonate is an organic compound comprising two phosphonic acid moieties (phosphonate, $-PO(OH)_2$) on a single carbon atom. The carbon atom may be further substituted with one or two side groups. Bisphosphonates suitable for medical practice are generally known, and can be generically defined by



wherein R1 and R2 are known side groups which determine the activity and pharmacological profile in generally known ways. R1 and R2 may independently be for example H, OH, Cl, Br, C1-C12 linear or branched, substituted or unsubstituted alkyl, C1-C12 linear or branched, substituted or unsubstituted aralkyl, C1-C12 linear or branched, substituted or unsubstituted heteroalkyl, C1-C12 linear or branched, substituted or unsubstituted arylalkyl. Examples of suitable bisphosphonates are

Agent	R_1 side chain	R_2 side chain
Etidronate	-OH	$-CH_3$
Clodronate	-Cl	-Cl
Tiludronate	-H	-S-  -Cl
Pamidronate	-OH	$-CH_2-CH_2-NH_2$
Neridronate	-OH	$-(CH_2)_5-NH_2$
Olpadronate	-OH	$-(CH_2)_2N(CH_3)_2$
Alendronate	-OH	$-(CH_2)_3-NH_2$
Ibandronate	-OH	$-CH_2-CH_2N(CH_3)(CH_2)_4-CH_3$
Risedronate	-OH	
Zoledronate	-OH	

Non-nitrogenous bisphosphonates are bisphosphonates which do not contain a nitrogen atom in either side group R1 or R2. Non-nitrogenous bisphosphonates are metabolised in the cell to compounds that replace the terminal pyrophosphate moiety of ATP, forming a non-functional molecule that competes with adenosine triphosphate (ATP) in the cellular energy metabolism. Examples of non nitrogenous bisphosphonates are Etidronate (R1 = OH, R2 = CH_3), Clodronate (R1 = R2 = Cl) and Tiludronate (R1 = 4-chlorophenylthio, R2=H).

Nitrogenous bisphosphonates are bisphosphonates which do contain a nitrogen atom in at least one side group R1 or R2. Nitrogenous bisphosphonates act on bone metabolism by binding and blocking the enzyme farnesyl diphosphate synthase (FPPS) in the HMG-CoA reductase pathway (also known as the mevalonate pathway). Examples of nitrogenous

bisphosphonates are Pamidronate (R1 = OH, R2=-$CH_2CH_2NH_2$), Neridronate (R1=OH, R2=$(CH_2)_5NH_2$), Olpadronate (R1=OH, R2=$(CH_2)_2N(CH_3)_2$, Alendronate (R1=OH, R2=$(CH_2)_3NH_2$, Ibandronate (R1=OH, R2=$(CH_2)_2N(CH_3)((CH_2)_4CH_3)$, Risedronate and Zoledronate.

Calcium ion has high affinity for a bisphosphonate, for which reason a bisphosphonate is a calcium ion solubilizer in the context of the present invention.

Calcium chelating compounds are also good calcium ion solubilizers. Calcium ion chelating compounds bind to calcium with high affinity. Calcium ion chelating compounds are well known. In the present context, they are bis-amino-(N,N,N,N) tetraacetic acid compounds, which are preferably linear, and which are further preferably non-aromatic. Calcium ion chelating compounds include for example ethylenediaminetetraacetic acid (EDTA), and ethylene glycol-bis(ß-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA).

Prodrugs are precursors which under physiological conditions are converted to the drug of interest. Prodrugs in the present context are ester prodrugs because of their increased lipophilicity. Increased lipophilicity enhances penetration of compounds in the brain. Esterification with a suitable group enhances lipophilicity. Upon entering of the brain, ester prodrugs are cleaved, releasing the original drug.

The present invention discloses a prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound. Such compounds can be called an ester prodrug for a bisphosphonate, or for a calcium chelating compound. Ester prodrugs of bisphosphonates or of

calcium chelating compounds may be linear or branched aliphatic C4 - C32 esters of bisphosphonates or calcium chelating compounds, preferably pentaoate, heptanoate or decanoate esters, or pivaloyl esters. A prodrug of the invention preferably has a lipophilicity, expressed as logP, of at least 0, at least 1, more preferably at least 2, more preferably at least 3. The upper limit of the lipophilicity is preferably 5. A much preferred lipophilicity is 0-5 preferably 1-5. A prodrug of the invention further preferably has a molecular weight ("MW") of less than 750, preferably less than 500.

A prodrug of the invention is preferably an ester of a bisphosphonate or an ester of a calcium chelating compound, which ester has a log P of at least 0, preferably at least 1, and a molecular weight of less than 750, preferably less than 500. Esters can be mono-, di-, tri-, tetra-, or (in the case of a bisphosphonate where R_1 is -OH) penta-esters. In preferred embodiments, the ester is a mono-, di- or tri-ester, most preferably a di-ester. For di-, tri-, tetra-, or (in the case of a bisphosphonate where R_1 is -OH) penta-esters, the ester groups on the base bisphosphonate or calcium chelating compound may be the same or different.

An ester of a bisphosphonate, in the present context, is a linear or branched aliphatic C4 - C32 ester of a bisphosphonate, preferably a C4-C22 ester, more preferably a C4 - C12 ester, and most preferably a pentyl ester, heptyl ester, decyl ester or 2,2-dimethylpropoyl ester.

An ester of a bisphosphonate can be prepared by esterification of the base bisphosphonate with a suitable alcohol, and subsequent purification. Suitable alcohols can be for example 2,2-dimethylpropanol, pentanol, heptanol or decanol.

In much preferred embodiments, the ester of a bisphosphonate is an etidronate ester, a clodronate ester, a tiludronate ester, a pamidronate ester, a neridronate ester, an olpadronate ester, an alendronate ester, an ibandronate ester, a risedronate ester or a zoledronate ester.

The ester of a bisphosphonate may be fully esterified (i.e. on all OH-groups which are available for esterification), or partially esteried (i.e. leaving some free OH groups available for esterification non-esterified). The optimal degree of esterification depends on the bisphosphonate in question, the type of ester group and the total molar mass of the bisphosphonate ester prodrug. The lipophilicity, expressed as logP, of the prodrug is preferably at least 0, more preferably at least 1, even more preferably at least 2, even more preferably at least 3. A much preferred lipophilicity is 0-5, preferably 1-5, more preferably 2-5, and even more preferably 3-5. The lipophilicity is preferably attained by esterification of the bisphosphonate. An ester of a bisphosphonate having a lipophilicity as described further preferably has a minimized molar mass. The molecular weight is preferably less than 750, more preferably less than 500. Bisphosphonate ester prodrugs having a small molar mass and a high lipophilicity are the most efficient bisphosphonate ester prodrugs to pass the blood brain barrier. For this reason, in some embodiments the ester of a bisphosphonate having lipophilicity as described is preferably a di-ester or a tri-ester, most preferably a di-ester.

The ester of a calcium chelating compound is a linear or branched aliphatic C4 - C32 ester of a calcium chelating compound, preferably a C4-C22 alkyl ester, more preferably a C4 - C12 ester, and most preferably a pentyl ester, heptyl ester, decyl ester or 2,2-dimethylpropoyl ester.
An ester of a calcium chelating compound can be prepared by esterification of the base calcium chelating compound with a suitable alcohol, and subsequent purification. Suitable alcohols can be for example 2,2-dimethylpropanol, pentanol, heptanol or decanol.
The calcium chelating compound is preferably a linear bis-amino-(N,N,N,N) tetraacetic acid compound, most preferably EDTA or EGTA. In much

preferred embodiments, the ester of a calcium chelating compound is an EDTA ester or an EGTA ester.

The calcium chelating compound may be fully esterified (i.e. on all acetic acid OH-groups), or partially esteried (i.e. leaving one or more free acetic acid OH groups). The optimal degree of esterification depends on the calcium chelating compound in question, the type of ester group and the total molar mass of the prodrug. The lipophilicity, expressed as logP, of the prodrug is preferably at least 0, more preferably at least 1, even more preferably at least 2, even more preferably at least 3. A much preferred lipophilicity is 0-5, preferably 1-5, more preferably 2-5, and even more preferably 3-5. The lipophilicity is preferably attained by esterification of the calcium chelating compound. An ester prodrug of a calcium chelating compound having a lipophilicity as described further preferably has a minimized molar mass. The molecular weight is preferably less than 750, more preferably less than 500. Calcium chelating compound ester prodrugs having a small molar mass and a high lipophilicity are the most efficient calcium chelating compound ester prodrugs to pass the blood brain barrier. For this reason, in some embodiments a calcium chelating compound ester prodrug having lipophilicity as described is preferably a mon-ester or a di-ester, preferably a mono-ester.

Lipophilicity of the prodrug can be determined by the octonanol/water partition coefficient, log P. The octanol/water partition coefficient can be determined by the shake-flask method, which consists of dissolving some of the agonist, antagonist or prodrug as the solute in question in a mixture of equal amounts of octanol and water, and then measuring the concentration of the solute in each solvent. The octanol/water partition coefficient is calculated by the ratio of the concentration of the solute in octanol, relative to the concentration in water, and expressed as ^{10}log value. The octanol/water partition coefficient is also referred to as logP.

An octonal/water partition coefficient of 0 means the solute is present at equal concentration in the octanol and water phases, whereas an octanol water partition coefficient of 2 means that the concentration of the solute in octanol is 100 times the concentration of the solute in water.

The prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer is preferably administered enterally, such as orally, sublingually, rectally or sublabially. Further preferably, the prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer is preferably administered parenterally, such as intravenously, intra-muscularly, intracerebrally, intracerebroventricularly, intrathecally or subcutaneously. In one embodiment, oral administration is preferred. In a further embodiment, intracerebral administration is preferred. In yet a further embodiment, intravenous administration is preferred. In all ways of administration, the ester prodrug for the calcium ion or magnesium ion solubilizer is preferably administered intermittently.

Intermittent administration is administration of the compound in single dosages, after which dosage a period of non-administration of the compound exists. The dosage may be administered as a single (bolus) dosage within 5 minutes, or which may be administered by prolonged dosing, such as a single dose administered over 5 minutes - 5 hours. Intermittent administration is preferably daily, two-daily, or weekly administration, most preferably daily administration.

Preferably, a single dosage is 0.01 - 5000 mg. This single dosage is preferably administered intermittently. In much preferred embodiments, administration is at a dosage of 0.01 - 5000 mg per day.

The ester prodrug for the calcium ion or magnesium ion solubilizer preferably passes blood brain barrier. This is particularly important for enteral and intravenous administration, in particular intravenous, oral, sublingual and sublabial administration. Passing the blood brain barrier means that the compound is capable of diffusing through the arteries in the brain, into the brain itself, in order to yield effective concentrations of the calcium ion or magnesium solubilizer by hydrolysis in the brain, so that concentrations of the calcium ion or magnesium ion solubilizer can be attained where clinical effects exceed side effects.

The invention furthermore discloses a method for treating a medical condition characterized by the presence of deposits of neuropathological peptides, preferably Alzheimer's disease, Parkinson's disease or Huntington's disease, comprising administering a prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound at an effective concentration, preferably at a dosage of 0.01 - 5000 mg per day. Said administration is preferably enteral use, such as oral, sublingual, rectal and sublabial use, or parenteral use, such as intravenous, intra-muscular, intracerebral, intracerebroventricular, intrathecal or subcutaneous use.

The invention furthermore discloses use of a prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound for the preparation of a medicament for the treatment of a medical condition characterized by the presence of deposits of neuropathological peptides, preferably Alzheimer's disease, Parkinson's disease or Huntington's disease.

For the purpose of clarity and a concise description features are described herein as part of the same or separate embodiments, however, it will be appreciated that the scope of the invention may include embodiments having combinations of all or some of the features described.

The invention will now be illustrated by the following, non-limiting examples.

Examples

Example 1: Effect of pamidronate and EDTA on extracellular post mortem TAU and Abeta levels.

Methods

Frozen cortical tissue was cut in 250 microm thin slices. Tissue was further chopped in 250 by 250 micron cubes by a McGalwin tissue chopper. Tissue was transferred to 20 milliliter glass vials and rinsed three times with calcium free krebs. 180 µl of tissue suspension was pipetted in a 96 well filtration plate and washed an additional time with calcium free krebs. Finally the tissue was incubated for 30 min with carbogenated calcium free krebs containing 2% bovine serum albumin to which control or study compound was spiked. Finally the filtrate was collected in 96 well plates and stored at -80 until analysis.

Analysis

Abeta and Tau in filtrates were analyzed using ELISA.

Results

Release of Amyloid beta or Tau from tissue of Alzheimer's patients was observed to be increased by EDTA and the biphosphonate Pamidronate. Pamidronate elevated release of Amyloid beta and tau more than EDTA.

These data indicate that EDTA and pamidronate facilitate dissolution of Abeta and Tau deposits in Alzheimer's brain tissue.

Example 2: ester prodrugs to penetrate the blood brain barrier.

It has been established that good brain penetration can be achieved using compounds which have a log P of at least 0, preferably at least 1, more preferably at least 2, even more preferably at least 3. A log P of between 0 and 5, preferably between 1 and 5, is preferred. It has further been established that good brain penetration can be achieved using compounds which have a molecular weight of lower than 750, preferably lower than 500.

Figure 1a - 1l shows various compounds. Preferred compounds in the context of the present invention are compounds 1c, 1d, 1e, 1g, 1j, 1k and 1l, most preferably 1c, 1d, 1g, 1j, 1k and 1l. All compounds can be prepared by esterification of the calcium ion or magnesium ion solubilizer and subsequent purification.

Figure	Compound	Log P	MW
1a	Pamidronate	-3.40	235.06
1b	pamidronate, mono-2,2-dimethylpropyl ester	-1.06	305.2
1c	pamidronate, di-2,2-dimethylpropyl ester	0.75	375.33
1d	pamidronate, tri-2,2-dimethylpropyl ester	3.09	445.46
1e	pamidronate, tetra-2,2-dimethylpropyl ester	4.90	515.60
1f	pamidronate, mono-2,2-dimethylpropyl ester	-0.96	305.2
1g	pamidronate, dipentyl ester	2.01	375.33
1h	Zoledronate	-2.83	286.11
1i	Zoledronate, mono-2,2-dimethylpropyl ester	0.56	340.24
1j	Zoledronate, di-2,2-dimethylpropyl ester	2.90	410.38
	Olpadronate	-2.77	263.12
	Olpadronate, mono-2,2-dimethylpropyl ester	-0.43	333.25
1k	Olpadronate, di-2,2-dimethylpropyl ester	1.91	403.38
	EDTA	-0.43	292.24
1l	EDTA, mono-2,2-dimethylpropyl ester	2.57	362.38

Claims

1. A prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound, for use in a method of treating a medical condition characterized by the presence of deposits of neuropathological peptides.
2. A prodrug for use according to claim 1, wherein the ester is a linear or branched aliphatic C4 - C32 ester of a bisphosphonate or of a calcium chelating compound.
3. A prodrug for use according to claim 1 or 2, wherein the prodrug has a lipophilicity, expressed as logP, of at least 0, preferably 1 - 5.
4. A prodrug according to any of claims 1 - 3, wherein the prodrug has a molecular weight of less than 750, preferably less than 500.
5. A prodrug for use according to any of claims 1 - 4, wherein the medical condition characterized by the presence of deposits of neuropathological peptides is Alzheimer's disease, Parkinson's disease or Huntington's disease.
6. A prodrug for use according to any of claims 1 - 5, wherein the ester of a bisphosphonate or the ester of a calcium chelating compound is administered intermittently.
7. A prodrug for use according to any of claims 1 - 6, wherein the ester of a bisphosphonate or the ester of a calcium chelating compound is an EDTA ester, an EGTA ester, an etidronate ester, a clodronate ester, a tiludronate ester, a pamidronate ester, a neridronate ester, an olpadronate ester, an alendronate ester, an ibandronate ester, a risedronate ester or a zoledronate ester.
8. A prodrug for use according to any of claims 1 - 7, wherein said use comprises enteral use, such as oral, sublingual, rectal and sublabial use, or parenteral use, such as intravenous, intra-muscular,

intracerebral, intracerebroventricular, intrathecal or subcutaneous use.

9. A prodrug for use according to any of claims 1 - 8, wherein said use is at a dosage of 0.01 - 5000 mg per day.

10. A prodrug for a physiologically acceptable calcium ion (Ca^{2+}) or magnesium ion (Mg^{2+}) solubilizer selected from an ester of a bisphosphonate or an ester of a calcium chelating compound, wherein the ester is a linear or branched aliphatic C4 - C32 ester of a bisphosphonate or of a calcium chelating compound, wherein the prodrug has a lipophilicity, expressed as log P, of at least 0, preferably at least 1.

11. A prodrug according to claim 10, wherein the prodrug has a molecular weight of less than 750, preferably less than 500.

12. A prodrug according to claim 10 or 11, wherein the prodrug is a bisphosphonate di-ester or tri-ester or a mono-ester for a calcium chelating compound.

13. A prodrug according to any of claims 10 - 12, wherein the prodrug is pamidronate di-2,2-dimethylpropyl ester, a pamidronate tri-2,2-dimethylpropyl ester, a pamidronate tetra-2,2-dimethylpropyl ester, a pamidronate dipentyl ester, a zoledronate, di-2,2-dimethylpropyl ester, an olpadronate di-2,2-dimethylpropyl ester or an EDTA mono-2,2-dimethylpropyl ester.

Figures

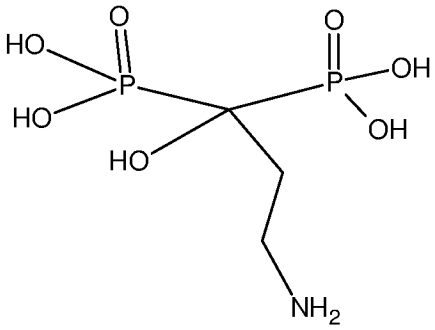


Figure 1a: pamidronate

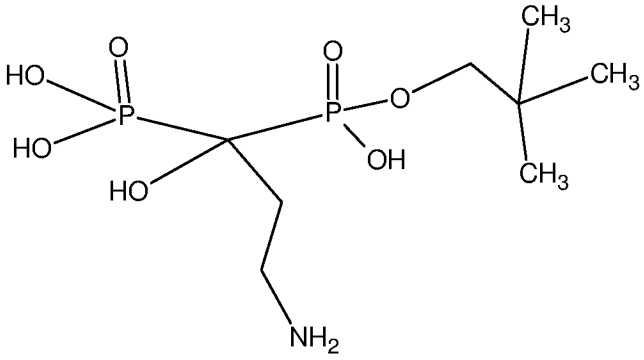


Figure 1b: pamidronate, mono-2,2-dimethylpropyl ester

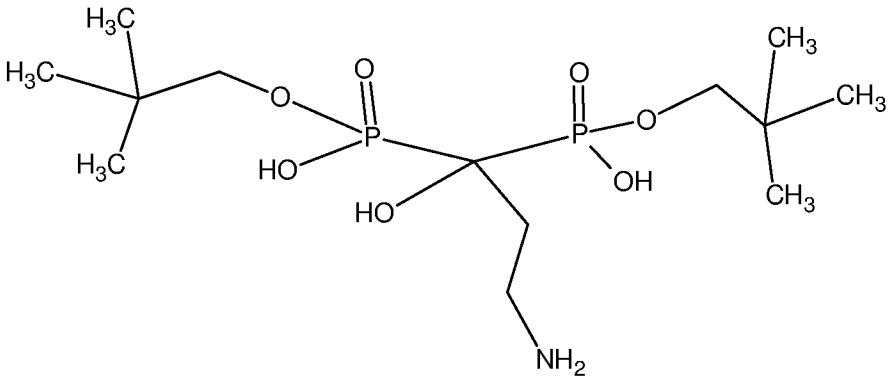
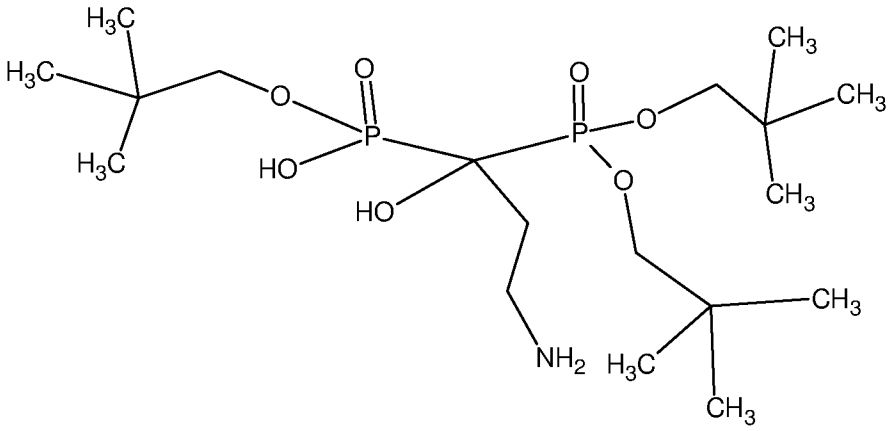
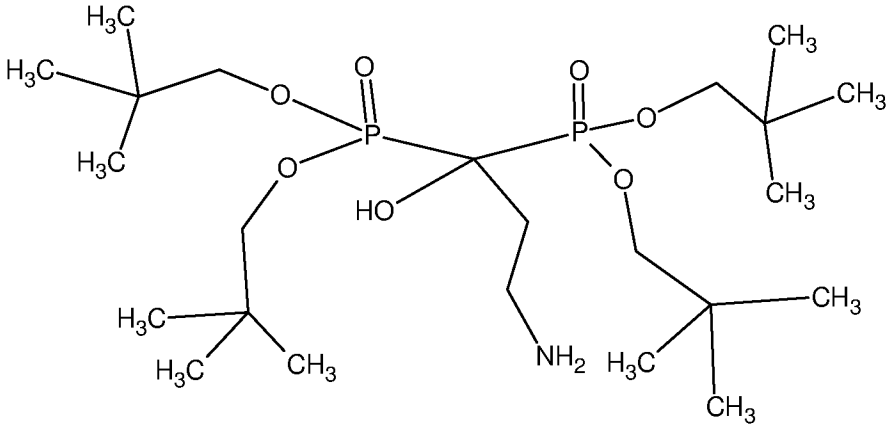


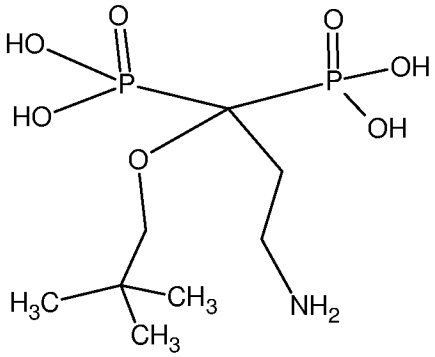
Figure 1c: pamidronate, di-2,2-dimethylpropyl ester



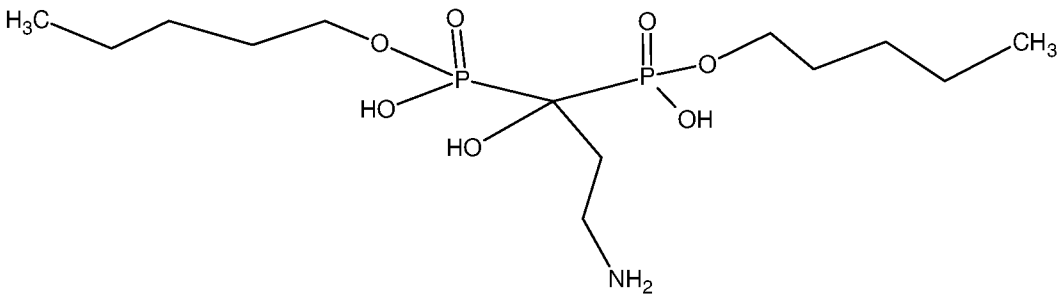
1d: pamidronate, tri-2,2-dimethylpropyl ester



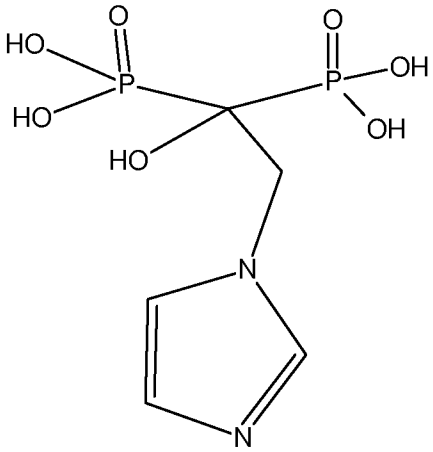
1e: pamidronate, tetra-2,2-dimethylpropyl ester



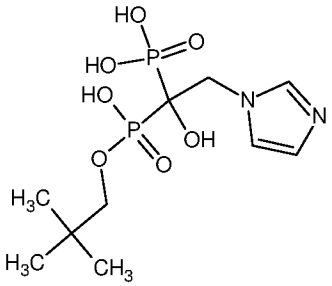
1f: pamidronate, mono-2,2-dimethylpropyl ester



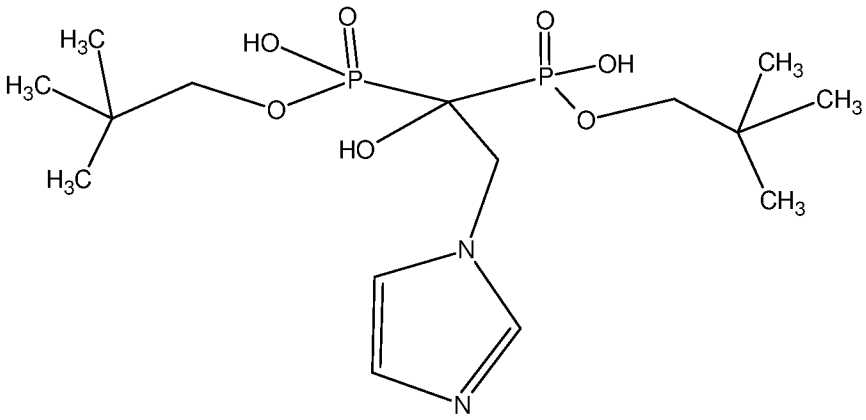
1g: pamidronate, dipentyl ester



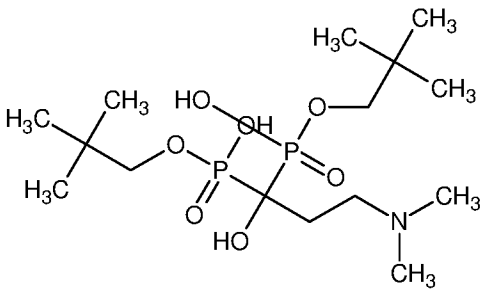
1h: zoledronate



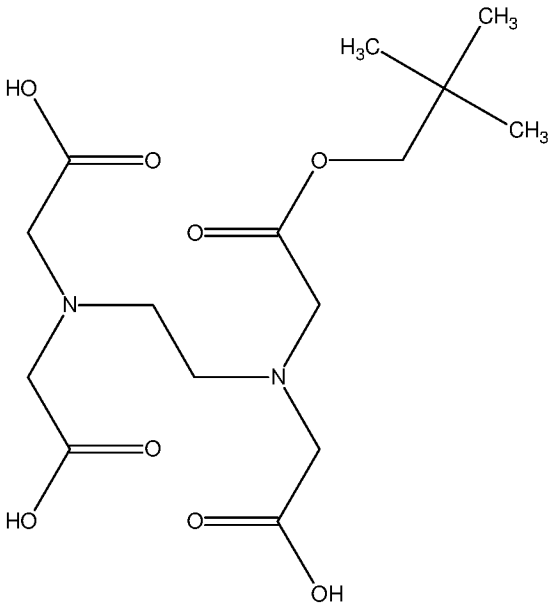
1i: zoledronate, mono-2,2-dimethylpropyl ester



1j: zoledronate, di-2,2-dimethylpropyl ester



1k: olpadronate, di-2,2-dimethylpropyl ester



1l: EDTA, mono-2,2-dimethylpropyl ester